Nuclear Medicine, Diagnostic Tomography and Imaging:

X-ray, CAT, Scanning, PET, FFT Imaging and Microscopy

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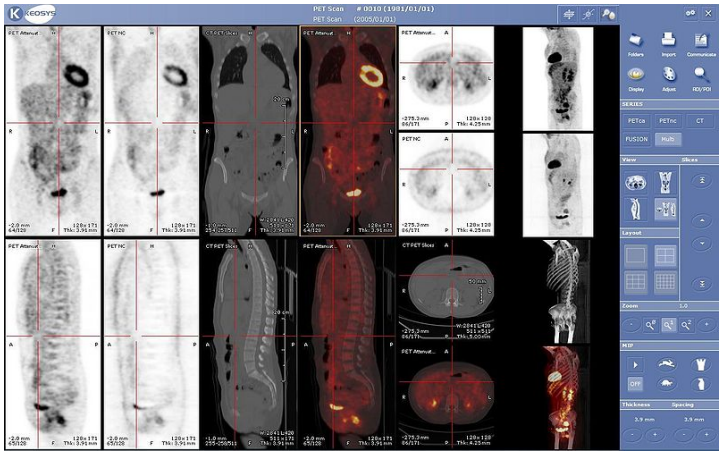
Nuclear medicine

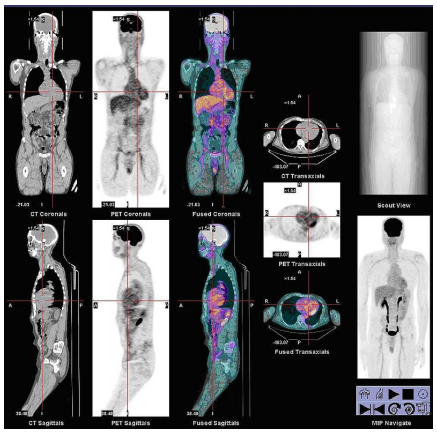
Nuclear medicine is a branch or specialty of medicine and medical imaging that uses radionuclides and relies on the process of radioactive decay in the diagnosis and treatment of disease.

In nuclear medicine procedures, radionuclides are combined with other chemical compounds or pharmaceuticals to form radiopharmaceuticals. These radiopharmaceuticals, once administered to the patient, can localize to specific organs or cellular receptors. This property of radiopharmaceuticals allows nuclear medicine the ability to image the extent of a disease-process in the body, based on the cellular function and physiology, rather than relying on physical changes in the tissue anatomy. In some diseases nuclear medicine studies can identify medical problems at an earlier stage than other diagnostic tests.

Treatment of disease, based on metabolism or uptake or binding of a ligand, may also be accomplished, similar to other areas of pharmacology. However, radiopharmaceuticals rely on the tissue-destructive power of short-range ionizing radiation.



A whole body PET/CT Fusion image



Normal whole body PET/CT scan with FDG-18. The whole body PET/CT scan is commonly used in the detection, staging and follow-up of various cancers.

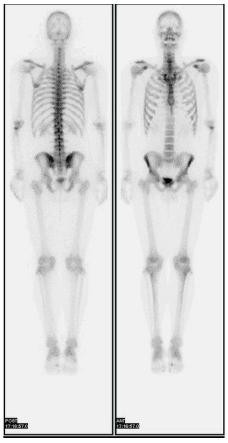
Description of the field

In nuclear medicine imaging, radiopharmaceuticals are taken internally, for example intravenously or orally. Then, external detectors (gamma cameras) capture and form images from the radiation emitted

by the radiopharmaceuticals. This process is unlike a diagnostic X-ray where external radiation is passed through the body to form an image.

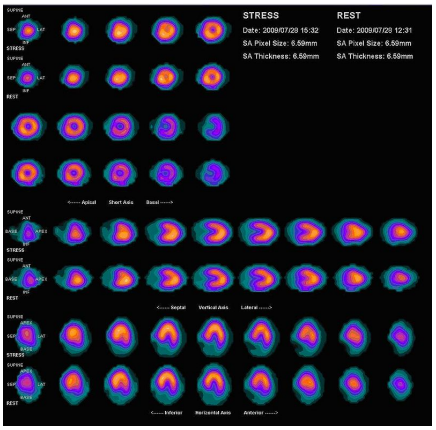
There are several techniques of diagnostic nuclear medicine. *Scintigraphy* ("scint") is the use of internal radionuclides to create two-dimensional[1] images. *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. *Positron emission tomography* (PET) uses coincidence detection to image functional processes.

Nuclear medicine tests differ from most other imaging modalities in that diagnostic tests primarily show the physiological function of the system being investigated as opposed to traditional anatomical imaging such as CT or MRI. Nuclear medicine imaging studies are generally more organ or tissue specific (e.g.: lungs scan, heart scan, bone scan, brain scan, etc.) than those in conventional radiology imaging, which focus on a particular section of the body (e.g.: chest X-ray, abdomen/pelvis CT scan, head CT scan, etc.). In addition, there are nuclear medicine studies that allow imaging of the whole body based on certain cellular receptors or functions. Examples are whole body PET scan or PET/CT scans, gallium scans, indium white blood cell scans, MIBG and octreotide scans.



A nuclear medicine whole body bone scan. The nuclear medicine whole body bone scan is generally used in evaluations of various bone related pathology, such as for bone pain, stress fracture, nonmalignant bone lesions, bone infections, or the spread of cancer to the bone.

While the ability of nuclear metabolism to image disease processes from differences in metabolism is unsurpassed, it is not unique. Certain techniques such as fMRI image tissues (particularly cerebral tissues) by blood flow, and thus show metabolism. Also, contrast-enhancement techniques in both CT and MRI show regions of tissue which are handling pharmaceuticals differently, due to an inflammatory process.

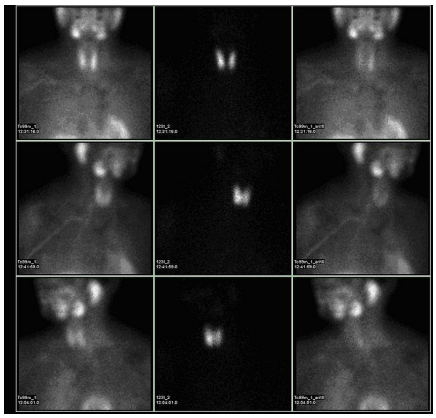


Nuclear Medicine myocardial perfusion scan with Thallium-201 for the rest images (bottom rows) and Tc-Sestamibi for the stress images (top rows). The nuclear medicine myocardial perfusion scan plays a pivotal role in the noninvasive evaluation of coronary artery disease. The study not only identifies patients with coronary artery disease, it also provides overall prognostic information or overall risk of adverse cardiac events for the patient.

Diagnostic tests in nuclear medicine exploit the way that the body handles substances differently when there is disease or pathology present. The radionuclide introduced into the body is often chemically bound to a complex that acts characteristically within the body; this is commonly known as a tracer. In the presence of disease, a tracer will often be distributed around the body and/or processed differently. For example, the ligand methylene-diphosphonate (MDP) can be preferentially taken up by bone. By chemically attaching technetium-99m to MDP, radioactivity can be transported and attached to bone via the hydroxyapatite for imaging. Any increased physiological function, such as due to a fracture in the bone, will usually mean increased concentration of the tracer. This often results in the appearance of a 'hot-spot' which is a focal increase in radio-accumulation, or a general increase in radio-accumulation throughout the physiological system. Some disease processes result in the exclusion of a tracer, resulting in the appearance of a 'cold-spot'. Many tracer complexes have been developed to image or treat many different organs, glands, and physiological processes.

Hybrid scanning techniques

In some centers, the nuclear medicine scans can be superimposed, using software or hybrid cameras, on images from modalities such as CT or MRI to highlight the part of the body in which the radiopharmaceutical is concentrated. This practice is often referred to as image fusion or co-registration, for example SPECT/CT and PET/CT. The fusion imaging technique in nuclear medicine provides information about the anatomy and function, which would otherwise be unavailable, or would require a more invasive procedure or surgery.

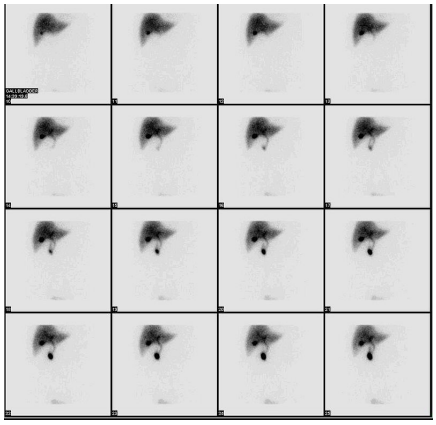


A nuclear medicine parathyroid scan demonstrates a parathyroid adenoma adjacent to the left inferior pole of the thyroid gland. . The above study was performed with Technetium-Sestamibi (1st column) and Iodine-123 (2nd column) simultaneous imaging and the subtraction technique (3rd column).

Practical concerns in nuclear imaging

The amount of radiation from diagnostic nuclear medicine procedures is kept within a safe limit and follows the "ALARA" (As Low As Reasonably Achievable) principle. The radiation dose from nuclear medicine imaging varies greatly depending on the type of study. The effective radiation dose can be lower than or comparable to the annual background radiation dose. It can also be in the range or higher than the radiation dose from an abdomen/pelvis CT scan.[2]

Some nuclear medicine procedures require special patient preparation before the study to obtain the most accurate result. Pre-imaging preparations may include dietary preparation or the withholding of certain medications. Patients are encouraged to consult with the nuclear medicine department prior to a scan.

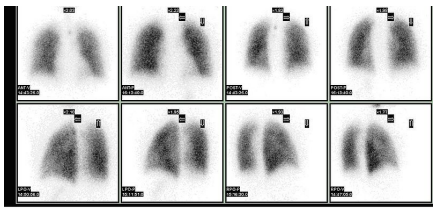


Normal hepatobiliary scan (HIDA scan). The nuclear medicine hepatobiliary scan is clinically useful in the detection of the gallbladder disease.

Nuclear medicine therapy

In nuclear medicine therapy, the radiation treatment dose is administered internally (e.g. intravenous or oral routes) rather from an external radiation source.

The radiopharmaceuticals used in Nuclear Medicine therapy emit ionizing radiation that travels only a short distance, thereby minimizing unwanted side effects and damage to noninvolved organs or nearby structures. Most Nuclear Medicine therapies can be performed as outpatient procedures since there are few side effects from the treatment and the radiation exposure to the general public can be kept within a safe limit. Common Nuclear Medicine therapies include 131I-sodium iodide for hyperthyroidism and thyroid cancer, Yttrium-90-ibritumomab tiuxetan (Zevalin) and Iodine-131-tositumomab (Bexxar) for refractory Lymphoma, ^{131}I-MIBG (metaiodobenzylguanidine) for neuroendocrine tumors, and palliative bone pain treatment with Samarium-153 or Strontium-89. In some centers the nuclear medicine department may also use implanted capsules of isotopes (brachytherapy) to treat cancer.

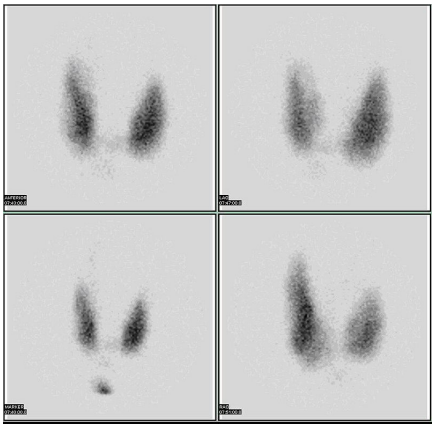


Normal pulmonary ventilation and perfusion (V/Q) scan. The nuclear medicine V/Q scan is useful in the evaluation of pulmonary embolism.

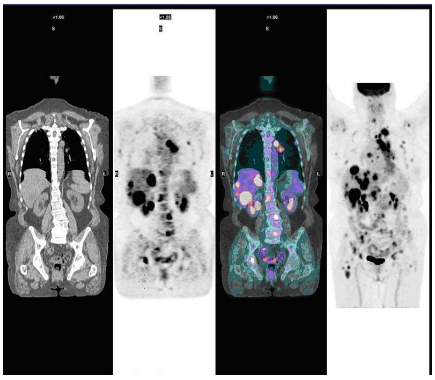
Most nuclear medicine therapies will also require appropriate patient preparation prior to a treatment. Therefore, consultation with the Nuclear Medicine department is recommended prior to therapy.

Molecular medicine

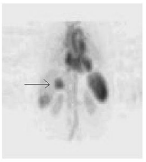
In the future, nuclear medicine may be known as molecular medicine. As our understanding of biological processes in the cells of living organism expands, specific probes can be developed to allow visualization, characterization, and quantification of biologic processes at the cellular and subcellular levels.[2] Nuclear Medicine is an ideal specialty to adapt to the new discipline of molecular medicine, because of its emphasis on function and its utilization of imaging agents that are specific for a particular disease process.



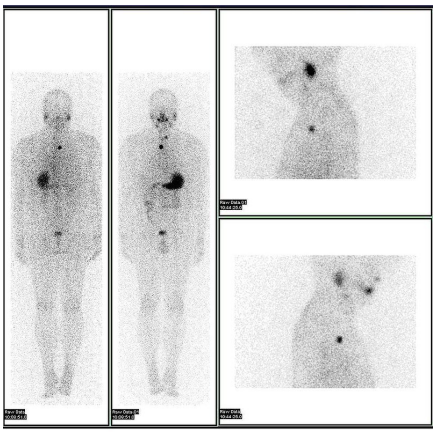
Thyroid scan with Iodine-123 for evaluation of hyperthyroidism.



Abnormal whole body PET/CT scan with multiple metastases from a cancer. The whole body PET/CT scan has became an important tool in the evaluation of cancer.



A nuclear medicine SPECT liver scan with technetium-99m labeled autologous red blood cells. A focus of high uptake (arrow) in the liver is consistent with a hemangioma.



Iodine-123 whole body scan for thyroid cancer evaluation. The study above was performed after the total thyroidectomy and TSH stimulation with thyroid hormone medication withdrawal. The study shows a small residual thyroid tissue in the neck and a mediastinum lesion, consistent with the thyroid cancer metastatic disease. The uptakes in the stomach and bowel are normal physiologic findings.

History

The history of nuclear medicine is rich with contributions from gifted scientists across different disciplines in physics, chemistry, engineering, and medicine. The multidisciplinary nature of Nuclear Medicine makes it difficult for medical historians to determine the birthdate of Nuclear Medicine. This can probably be best placed between the discovery of artificial radioactivity in 1934 and the production of radionuclides by Oak Ridge National Laboratory for medicine related use, in 1946.[3]

Many historians consider the discovery of artificially produced radionuclides by Frédéric Joliot-Curie and Irène Joliot-Curie in 1934 as the most significant milestone in Nuclear Medicine.[3] In February 1934, they reported the first artificial production of radioactive material in the Nature journal, after discovering radioactivity in aluminum foil that was irradiated with a polonium preparation. Their work built upon earlier discoveries by Wilhelm Konrad Roentgen for X-ray, Henri Becquerel for radioactive uranium salts, and Marie Curie (mother of Irene Curie) for radioactive thorium, polonium and coining the term "radioactivity." Taro Takemi studied the application of nuclear physics to medicine in the 1930s. The history of Nuclear Medicine will not be complete without mentioning these early pioneers.

Nuclear medicine gained public recognition as a potential specialty on December 7, 1946 when an article was published in the Journal of the American Medical Association by Sam Seidlin. The article described a successful treatment of a patient with thyroid cancer metastases using radioiodine (I-131). This is considered by many historians as the most important article ever published in Nuclear Medicine.[4] Although, the earliest use of I-131 was devoted to therapy of thyroid cancer, its use was later expanded to include imaging of the thyroid gland, quantification of the thyroid function, and therapy for hyperthyroidism.

Widespread clinical use of Nuclear Medicine began in the early 1950s, as knowledge expanded about radionuclides, detection of radioactivity, and using certain radionuclides to trace biochemical processes. Pioneering works by Benedict Cassen in developing the first rectilinear scanner and Hal O. Anger's scintillation camera (Anger camera) broadened the young discipline of Nuclear Medicine into a full-fledged medical imaging specialty.

In these years of Nuclear Medicine, the growth was phenomenal. The Society of Nuclear Medicine was formed in 1954 in Spokane, Washington, USA. In 1960, the Society began publication of the Journal of Nuclear Medicine, the premier scientific journal for the discipline in America. There was a flurry of research and development of new radionuclides and radiopharmaceuticals for use with the imaging devices and for in-vitro studies5.

Among many radionuclides that were discovered for medical-use, none were as important as the discovery and development of Technetium-99m. It was first discovered in 1937 by C. Perrier and E. Segre as an artificial element to fill space number 43 in the Periodic Table. The development of generator system to produce Technetium-99m in the 1960s became a practical method for medical use. Today, Technetium-99m is the most utilized element in Nuclear Medicine and is employed in a wide variety of Nuclear Medicine imaging studies.

By the 1970s most organs of the body could be visualized using Nuclear Medicine procedures. In 1971, American Medical Association officially recognized nuclear medicine as a medical specialty.[5] In 1972, the American Board of Nuclear Medicine was established, cementing Nuclear Medicine as a medical specialty.

In the 1980s, radiopharmaceuticals were designed for use in diagnosis of heart disease. The development of single photon emission tomography, around the same time, led to three-dimensional reconstruction of the heart and establishment of the field of Nuclear Cardiology.

More recent developments in Nuclear Medicine include the invention of the first positron emission tomography scanner (PET). The concept of emission and transmission tomography, later developed into single photon emission computed tomography (SPECT), was introduced by David E. Kuhl and Roy Edwards in the late 1950s . Their work led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed at the Washington University School of Medicine. These innovations led to fusion imaging with SPECT and CT by Bruce Hasegawa from University of California San Francisco (UCSF), and the first PET/CT prototype by D. W. Townsend from University of Pittsburgh in 1998 .

PET and PET/CT imaging experienced slower growth in its early years owing to the cost of the modality and the requirement for an on-site or nearby cyclotron. However, an administrative decision to approve medical reimbursement of limited PET and PET/CT applications in oncology has led to phenomenal growth and widespread acceptance over the last few years. PET/CT imaging is now an integral part of oncology for diagnosis, staging and treatment monitoring.

Source of radionuclides, with notes on a few radiopharmaceuticals

About a third of the world's supply, and most of North America's supply, of medical isotopes are produced at the Chalk River Laboratories in Chalk River, Ontario, Canada. (Another third of the world's supply, and most of Europe's supply, are produced at the Petten nuclear reactor in the Netherlands.) The Canadian Nuclear Safety Commission ordered the NRU reactor to be shut down on November 18, 2007 for regularly scheduled maintenance and an upgrade of the safety systems to modern standards. The upgrade took longer than expected and in December 2007 a critical shortage of medical isotopes occurred. The Canadian government unanimously passed emergency legislation, allowing the reactor to re-start on 16 December 2007, and production of medical isotopes to continue.

The Chalk River reactor is used to irradiate materials with neutrons which are produced in great quantity during the fission of U-235. These neutrons change the nucleus of the irradiated material by adding a neutron, or by splitting it in the process of nuclear fission. In a reactor, one of the fission products of uranium is molybdenum-99 which is extracted and shipped to radiopharmaceutical houses all over North America. The Mo-99 radioactively beta decays with a half-life of 2.7 days, turning initially into Tc-99m, which is then extracted (milked) from a "moly cow" (see technetium-99m generator). The Tc-99m then further decays, while inside a patient, releasing a gamma photon which is detected by the gamma camera. It decays to its ground state of Tc-99, which is relatively non-radioactive compared to Tc-99m.

The most commonly used radioisotope in PET F-18, is not produced in any nuclear reactor, but rather in a circular acclererator called a cyclotron. The cyclotron is used to accelerate protons to bombard the stable heavy isotope of oxygen O-18. The O-18 constitutes about 0.20% of ordinary oxygen (mostly O-16), from which it is extracted. The F-18 is then typically used to make FDG (see this link for more information on this process).

Common isotopes used in nuclear medicine

isotope	symbol	Z	$T_{1/2}$	decay	photons	β
Imaging:						
fluorine-18	^{18}F	9	109.77 m	β^+	511 (193%)	0.664 (97%)
gallium-67	^{67}Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
krypton-81m	^{81m}Kr	36	13.1 s	IT	190 (68%)	-
rubidium-82	^{82}Rb	37	1.27 m	β^+	511 (191%)	3.379 (95%)
technetium-99m	^{99m}Tc	43	6.01 h	IT	140 (89%)	-
indium-111	^{111}In	49	2.80 d	ec	171 (90%), 245 (94%)	-
iodine-123	^{123}I	53	13.3 h	ec	159 (83%)	-
xenon-133	^{133}Xe	54	5.24 d	β^-	81 (31%)	0.364 (99%)
thallium-201	^{201}Tl	81	3.04 d	ec	69–83* (94%), 167 (10%)	-
Therapy:						
yttrium-90	^{90}Y	39	2.67 d	β^-	-	2.280 (100%)
iodine-131	^{131}I	53	8.02 d	β^-	364 (81%)	0.807 (100%)

Z = atomic number, the number of protons; $T_{1/2}$ = half-life; decay = mode of decay
photons = principle photon energies in kilo-electron volts, keV, (abundance/decay)
β = beta maximum energy in mega-electron volts, MeV, (abundance/decay)
$\beta^+ = \beta^+$ decay; $\beta^- = \beta^-$ decay; IT = isomeric transition; ec = electron capture
* X-rays from progeny, mercury, Hg

A typical nuclear medicine study involves administration of a radionuclide into the body by intravenous injection in liquid or aggregate form, ingestion while combined with food, inhalation as a gas or aerosol, or rarely, injection of a radionuclide that has undergone micro-encapsulation. Some studies require the labeling of a patient's own blood cells with a radionuclide (leukocyte scintigraphy and red blood cell scintigraphy). Most diagnostic radionuclides emit gamma rays, while the cell-damaging properties of beta particles are used in therapeutic applications. Refined radionuclides for use in nuclear medicine are derived from fission or fusion processes in nuclear reactors, which produce radionuclides with longer half-lives, or cyclotrons, which produce radionuclides with shorter half-lives, or take advantage of natural decay processes in dedicated generators, i.e. molybdenum/technetium or strontium/rubidium.

The most commonly used intravenous radionuclides are:

- Technetium-99m (technetium-99m)
- Iodine-123 and 131

- Thallium-201
- Gallium-67
- Fluorine-18 Fluorodeoxyglucose
- Indium-111 Labeled Leukocytes

The most commonly used gaseous/aerosol radionuclides are:

- Xenon-133
- Krypton-81m
- Technetium-99m Technegas [6]
- Technetium-99m DTPA

Analysis

The end result of the nuclear medicine imaging process is a "dataset" comprising one or more images. In multi-image datasets the array of images may represent a time sequence (i.e. cine or movie) often called a "dynamic" dataset, a cardiac gated time sequence, or a spatial sequence where the gamma-camera is moved relative to the patient. SPECT (single photon emission computed tomography) is the process by which images acquired from a rotating gamma-camera are reconstructed to produce an image of a "slice" through the patient at a particular position. A collection of parallel slices form a slice-stack, a three-dimensional representation of the distribution of radionuclide in the patient.

The nuclear medicine computer may require millions of lines of source code to provide quantitative analysis packages for each of the specific imaging techniques available in nuclear medicine.

Time sequences can be further analysed using kinetic models such as multi-compartment models or a Patlak plot.

Radiation dose

A patient undergoing a nuclear medicine procedure will receive a radiation dose. Under present international guidelines it is assumed that any radiation dose, however small, presents a risk. The radiation doses delivered to a patient in a nuclear medicine investigation present a very small risk of inducing cancer. In this respect it is similar to the risk from X-ray investigations except that the dose is delivered internally rather than from an external source such as an X-ray machine.

The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sieverts (usually given in millisieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerels (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

Effective doses can range from 6 μSv (0.006 mSv) for a 3 MBq chromium-51 EDTA measurement of glomerular filtration rate to 37 mSv for a 150 MBq thallium-201 non-specific tumour imaging procedure. The common bone scan with 600 MBq of technetium-99m-MDP has an effective dose of approximately 3.5 mSv (1).

Formerly, units of measurement were the curie (Ci), being 3.7E10 Bq, and also 1.0 grams of Radium (Ra-226); the rad (radiation absorbed dose), now replaced by the gray; and the rem (Röntgen equivalent man), now replaced with the sievert. The rad and rem are essentially equivalent for almost all nuclear medicine procedures, and only alpha radiation will produce a higher Rem or Sv value, due to its much higher Relative Biological Effectiveness (RBE). Alpha emitters are nowadays rarely used in nuclear medicine, but were used extensively before the advent of nuclear reactor and accelerator produced radionuclides. The concepts involved in radiation exposure to humans is covered by the field of Health Physics.

Nuclear Medicine Careers

Nuclear Medicine Technologist

The information below is adapted from the Society of Nuclear Medicine (SNM) website on a scientist career. For more information and educational requirements, please see training [7]

The nuclear medicine scientist works closely with the nuclear medicine physician. Some of the scientist's primary responsibilities are to:

- Prepare and administer radioactive chemical compounds, known as radiopharmaceuticals
- Perform patient imaging procedures using sophisticated radiation-detecting instrumentation
- Accomplish computer processing and image enhancement
- Analyze biologic specimens in the laboratory
- Provide images, data analysis, and patient information to the physician for diagnostic interpretation.

During an imaging procedure, the scientist works directly with the patient. The scientist:

- Gains the patient's confidence by obtaining pertinent history, describing the procedure and answering any questions
- Monitors the patient's physical condition during the course of the procedure
- Notes any specific patient's comments which might indicate the need for additional images or might be useful to the physician in interpreting the results of the procedure.

Nuclear medicine scientists work in a wide variety of clinical settings, such as

- Community hospitals
- University-affiliated teaching hospitals and medical centers
- Outpatient imaging facilities
- Public health institutions
- Government and private research institutes.

The physician career in nuclear medicine

Nuclear medicine physicians are primarily responsible for interpretation of diagnostic nuclear medicine scans and treatment of certain diseases, such as cancer, thyroid disease and palliative bone pain.

There are a variety of reasons why physicians have chosen to specialize in nuclear medicine. Some became nuclear medicine physicians because of their interest in nuclear physics and medical imaging. Others may have switched to nuclear medicine after training in other specialties, because of the regular work hours (on average about 8 to 10 hours a day). Others have chosen nuclear medicine because of research opportunities in molecular medicine or molecular imaging.

Nuclear medicine physicians frequently interact with other specialties in medicine and consult on a variety of clinical cases. A nuclear medicine report may save a patient from more invasive or high risk procedures, and/or lead to early disease diagnosis. Nuclear Medicine physicians can be called upon to consult on complex or equivocal clinical cases. Aside from consultations with other physicians, nuclear physicians may directly interact with patients through various nuclear medicine therapies (e.g.: I131 thyroid therapy, refractory lymphoma treatment, palliative bone pain therapy).

A disadvantage of a nuclear medicine career for a physician is that it suffers from low job turnover and a small job market, owing to the specialized nature of the field. Advantages of the field include job satisfaction and more regular hours than many fields of medicine, since very rarely are the procedures in this field performed on an emergency basis.

Nuclear medicine residency/training (physicians)

The information below is adapted from the American Board of Nuclear Medicine (ABNM). For more information, please see ABNM [8]

General professional education requirement in the United States of America: graduation from a medical school approved by the Liaison Committee on Medical Education or the American Association of Colleges of Osteopathic Medicine.

In USA the post-doctoral training in nuclear medicine can be approached from three different pathways:

1. If the person has successfully completed an accredited radiology residency then additional ONE year of training in Nuclear Medicine is required to be eligible for ABNM board certification.
2. If the person has successfully completed a clinical residency (e.g. Internal Medicine, Family Medicine, Surgery, Neurology, etc.) then an additional TWO years of training in Nuclear Medicine is required to be eligible for ABNM board certification.
3. If the person has successfully completed one year of preparatory post-doctoral training (internship) then an additional THREE years of training in Nuclear Medicine is required to be eligible for ABNM board certification.

See also

- Background radiation
- Human experimentation in the United States
- Radiology

Notes

[1] thefreedictionary.com > scintigraphy (http://medical-dictionary.thefreedictionary.com/scintigraphy) Citing: Dorland's Medical Dictionary for Health Consumers, 2007 by Saunders; Saunders Comprehensive Veterinary Dictionary, 3 ed. 2007; McGraw-Hill Concise Dictionary of Modern Medicine, 2002 by The McGraw-Hill Companies
[2] [www.molecularimagingcenter.org], Gambhir S. Just what is molecular medicine.
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[5] http://interactive.snm.org/docs/whatisnucmed.pdf from the Society of Nuclear Medicine.
[6] http://jcsmr.anu.edu.au/technegas/home.html
[7] Training (http://interactive.snm.org/index.cfm?PageID=985&RPID=193)
[8] Acgme (http://www.acgme.org/acWebsite/navPages/nav_200.asp)

Further reading

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- Taylor A, Schuster DM, Naomi Alazraki N: A Clinicians' Guide to Nuclear Medicine, 2nd edition. Society of Nuclear Medicine, 2000. ISBN 978-0932004727
- Mark J. Shumate MJ, Kooby DA, Alazraki NP: A Clinician's Guide to Nuclear Oncology: Practical Molecular Imaging and Radionuclide Therapies. Society of Nuclear Medicine, January 2007. ISBN 978-0972647885
- Ell P, Gambhir S: Nuclear Medicine in Clinical Diagnosis and Treatment. Churchill Livingstone, 2004. (1950 pages) ISBN 978-0443073120

External links

- Society of Nuclear Medicine (http://www.snm.org/)
- Brochure: What is Nuclear Medicine? (http://interactive.snm.org/docs/whatisnucmed.pdf)
- Resource center: information about nuclear medicine (http://interactive.snm.org/index.cfm?PageID=6309&RPID=1089)
- International Atomic Energy Agency (IAEA), Division of Human Health, Nuclear Medicine (http://www-naweb.iaea.org/nahu/nm/default.asp)
- RADAR Medical Procedure Radiation Dose Calculator and Consent Language Generator (http://www.doseinfo-radar.com/RADARDoseRiskCalc.html)
- Association of Image Producers and Equipment Suppliers (http://www.aipes-eeig.org/)

Radiobiology

Radiobiology (or *radiation biology*) is the interdisciplinary field of science that studies the biological effects of ionizing and non-ionizing radiation of the whole electromagnetic spectrum, including radioactivity (alpha, beta and gamma), x-rays, ultraviolet radiation, visible light, microwaves, radio wave, low-frequency radiation (such as used in alternate electric transmission, ultrasound thermal radiation (heat), and related modalities. It is a subset of biophysics.

Areas of interest

The interactions between electromagnetic fields (EMF) and organisms can be studied at several levels:

- radiation physics
- radiation chemistry
- molecular and cell biology
- molecular genetics
- cell death and apoptosis
- dose modifying agents
- protection and repair mechanisms
- tissue responses to radiation
- radio-adaptation of living organisms
- high and low-level electromagnetic radiation and health
- specific absorption rates of organisms
- radiation poisoning
- radiation oncology (radiation therapy in cancer)

Radiobiology of non-ionizing radiation includes:

- Bioelectromagnetics
- Magnetobiology

Radiation sources for radiobiology

Radiobiology experiments typically make use of a radiation source which could be:

- An isotopic source, typically ^{137}Cs or ^{60}Co.
- A particle accelerator generating high energy protons, electrons or charged ions. Biological samples can be irradiated using either a broad, uniform beam[1] or using a microbeam, focused down to cellular or subcellular sizes.
- A UV lamp.

See also

- Radiosensitivity
- Radiology
- Nuclear medicine
- Radioactivity in biology
- Radiophobia
- Cell survival curve
- Relative biological effectiveness
- Health threat from cosmic rays
- Background radiation

Notes

[1] Pattison, J. E., Hugtenburg, R. P., Beddoe, A. H. and Charles, M. W. (2001), Experimental Simulation of A-bomb Gamma-ray Spectra for Radiobiology Studies, *Radiation Protection Dosimetry* **95**(2):125-136.

References and further reading

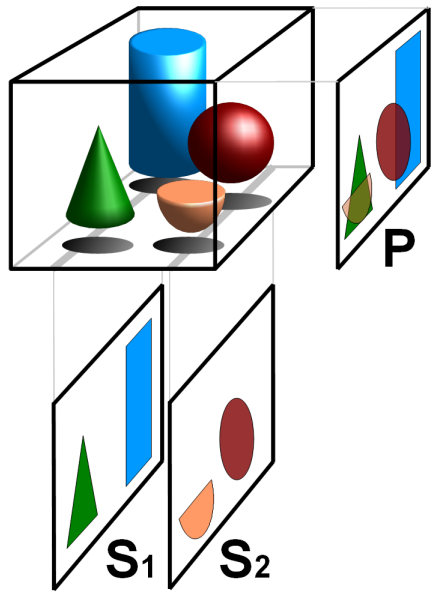
- WikiMindMap (http://www.wikimindmap.org/viewmap.php?wiki=en.wikipedia.org&topic=radiobiology)
- Eric Hall, *Radiobiology for the Radiobiologist*. 2006. Lippincott
- G.Gordon Steel, "Basic Clinical Radiobiology". 2002. Hodder Arnold.
- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html)

External links

- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html)

Tomography

Tomography is imaging by sections or sectioning, through the use of any kind of penetrating wave. A device used in tomography is called a **tomograph**, while the image produced is a **tomogram**. The method is used in radiology, archaeology, biology, geophysics, oceanography, materials science, astrophysics and other sciences. In most cases it is based on the mathematical procedure called **tomographic reconstruction**. The word was derived from the Greek word *tomos* which means "part" or "section", representing the idea of "a section", "a slice" or "a cutting". A tomography of several sections of the body is known as a polytomography.



Basic principle of tomography: superposition free tomographic cross sections S_1 and S_2 compared with the projected image P

Etymology

The word "tomography" is derived from the Greek tomos (part) and graphein (to write).

Description

In conventional medical X-ray tomography, clinical staff make a sectional image through a body by moving an X-ray source and the film in opposite directions during the exposure. Consequently, structures in the focal plane appear sharper, while structures in other planes appear blurred.[1] By modifying the direction and extent of the movement, operators can select different focal planes which contain the structures of interest. Before the advent of more modern computer-assisted techniques, this technique, ideated in the 1930s by the radiologist Alessandro Vallebona, proved useful in reducing the problem of superimposition of structures in projectional (shadow) radiography.

Modern tomography

More modern variations of tomography involve gathering projection data from multiple directions and feeding the data into a tomographic reconstruction software algorithm processed by a computer.[2] Different types of signal acquisition can be used in similar calculation algorithms in order to create a tomographic image. With current 2005 technology, tomograms are derived using several different physical phenomena listed in the following table.

Physical phenomenon	Type of tomogram
X-rays	CT
gamma rays	SPECT
radio-frequency waves	MRI
electron-positron annihilation	PET
electrons	Electron tomography or 3D TEM
ions	atom probe

Some recent advances rely on using simultaneously integrated physical phenomena, e.g. X-rays for both CT and angiography, combined CT/MRI and combined CT/PET.

The term *volume imaging* might subsume these technologies more accurately than the term *tomography*. However, in the majority of cases in clinical routine, staff request output from these procedures as 2-D slice images. As more and more clinical decisions come to depend on more advanced volume visualization techniques, the terms *tomography/tomogram* may go out of fashion.

Many different reconstruction algorithms exist. Most algorithms fall into one of two categories: filtered back projection (FBP) and iterative reconstruction (IR). These procedures give inexact results: they represent a compromise between accuracy and computation time required. FBP demands fewer computational resources, while IR generally produces fewer artifacts (errors in the reconstruction) at a higher computing cost.

Although MRI and ultrasound make cross sectional images they don't acquire data from different directions. In MRI spatial information is obtained by using magnetic fields. In ultrasound, spatial information is obtained simply by focusing and aiming a pulsed ultrasound beam.

Synchrotron X-ray tomographic microscopy

Recently a new technique called synchrotron X-ray tomographic microscopy (SRXTM) allows for detailed three dimensional scanning of fossils.

Types of tomography

Name	Source of data	Abbreviation	Year of introduction
Atom probe tomography	Atom probe	APT	
Confocal microscopy (Laser scanning confocal microscopy)	Laser scanning confocal microscopy	LSCM	
Cryo-electron tomography	Cryo-electron microscopy	Cryo-ET	
Electrical capacitance tomography	Electrical capacitance	ECT	
Electrical resistivity tomography	Electrical resistivity	ERT	
Electrical impedance tomography	Electrical impedance	EIT	1984
Functional magnetic resonance imaging	Magnetic resonance	fMRI	1992
Magnetic induction tomography	Magnetic induction	MIT	
Magnetic resonance imaging or nuclear magnetic resonance tomography	Nuclear magnetic moment	MRI or MRT	
Neutron tomography	Neutron		
Ocean acoustic tomography	Sonar		
Optical coherence tomography	Interferometry	OCT	
Optical projection tomography	Optical microscope	OPT	
Photoacoustic imaging in biomedicine	Photoacoustic spectroscopy	PAT	
Positron emission tomography	Positron emission	PET	
Positron emission tomography - computed tomography	Positron emission & X-ray	PET-CT	
Quantum tomography	Quantum state		
Single photon emission computed tomography	Gamma ray	SPECT	
Seismic tomography	Ground-penetrating radar		
Thermoacoustic imaging	Photoacoustic spectroscopy	TAT	
Ultrasound-modulated optical tomography	Ultrasound	UOT	

Ultrasound transmission tomography	Ultrasound		
X-ray tomography	X-ray	CT, CATScan	1971
Zeeman-Doppler imaging	Zeeman effect		

Discrete tomography and Process tomography refer to processing techniques.

See also

- Chemical imaging
- Geophysical imaging
- Medical imaging
- MRI compared with CT
- Network tomography
- Nonogram, a type of puzzle based on a discrete model of tomography
- Radon transform
- Tomographic reconstruction

References

[1] MeSH *Tomography* (http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Tomography)

[2] Herman, G. T., Fundamentals of computerized tomography: Image reconstruction from projection, 2nd edition, Springer, 2009

External links

- International Journal of Tomography & Statistics (IJTS) (http://www.isder.ceser.res.in/ijts.html)
- Microtomography/Synchrotron tomography (http://www.bronnikov-algorithms.com/downloads/Andrei.Bronnikov_Image_reconstruction.pdf)

X-ray computed tomography

Computed tomography (CT) is a medical imaging method employing tomography created by computer processing.[1] Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation.[2]

A patient is receiving a CT scan for cancer. Outside of the scanning room is an imaging computer that reveals a 3D image of the body's interior.

CT produces a volume of data which can be manipulated, through a process known as "windowing", in order to demonstrate various bodily structures based on their ability to block the X-ray beam. Although historically the images generated were in the axial or transverse plane, orthogonal to the long axis of the body, modern scanners allow this volume of data to be reformatted in various planes or even as volumetric (3D) representations of structures. Although most common in medicine, CT is also used in other fields, such as nondestructive materials testing. Another example is archaeological uses such as imaging the contents of sarcophagi or the DigiMorph project at the University of Texas at Austin which uses a CT scanner to study biological and paleontological specimens.

Usage of CT has increased dramatically over the last two decades[3] . An estimated 72 million scans were performed in the United States in 2007.[4]

Terminology

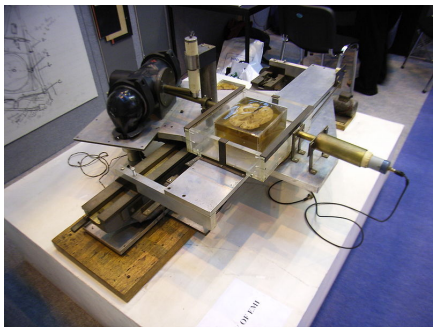
The word "tomography" is derived from the Greek *tomos* (slice) and *graphein* (to write). Computed tomography was originally known as the "EMI scan" as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as **computed axial tomography** (CAT or CT scan) and **body section röntgenography**.

Although the term "computed tomography" could be used to describe positron emission tomography and single photon emission computed tomography, in practice it usually refers to the computation of tomography from X-ray images, especially in older medical literature and smaller medical facilities.

In MeSH, "computed axial tomography" was used from 1977–79, but the current indexing explicitly includes "X-ray" in the title.[5]

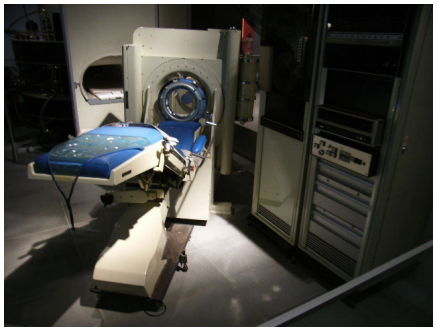
History

In the early 1900s, the Italian radiologist Alessandro Vallebona proposed a method to represent a single slice of the body on the radiographic film. This method was known as tomography. The idea is based on simple principles of projective geometry: moving synchronously and in opposite directions the X-ray tube and the film, which are connected together by a rod whose pivot point is the focus; the image created by the points on the focal plane appears sharper, while the images of the other points annihilate as noise. This is only marginally effective, as blurring occurs only in the "x" plane. There are also more complex devices which can move in more than one plane and perform more effective blurring.



The prototype CT scanner

Tomography had been one of the pillars of radiologic diagnostics until the late 1970s, when the availability of minicomputers and of the transverse axial scanning method, this last due to the work of Godfrey Hounsfield and South African-born Allan McLeod Cormack, gradually supplanted it as the modality of CT. Mathematically, the method is based upon the use of the Radon Transform invented by Johann Radon in 1917. But as Cormack remembered later[6] , he had to find the solution himself since it was only in 1972, that he learned of the work of Radon, by chance.



A historic EMI-Scanner

The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom at EMI Central Research Laboratories using X-rays. Hounsfield conceived his idea in 1967.[7] The first EMI-Scanner was installed in Atkinson Morley Hospital in Wimbledon, England, and the first patient brain-scan was done on 1 October 1971[8] . It was publicly announced in 1972.

The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over 5 minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer. The scanner had a single photomultiplier detector, and operated on the Translate/Rotate principle.[8]

It has been claimed that thanks to the success of The Beatles, EMI could fund research and build early models for medical use.[9] The first production X-ray CT machine (in fact called the "EMI-Scanner") was limited to making tomographic sections of the brain, but acquired the image data in about 4 minutes (scanning two adjacent slices), and the computation time (using a Data General Nova minicomputer) was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank was used to reduce the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 x 80 pixels.

In the U.S., the first installation was at the Mayo Clinic. As a tribute to the impact of this system on medical imaging the Mayo Clinic has an EMI scanner on display in the Radiology Department. Allan McLeod Cormack of Tufts University in Massachusetts independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine.[10]

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS, at Georgetown University. This machine had 30 photomultiplier tubes as detectors and completed a scan in only 9 translate/rotate cycles, much faster than the EMI-scanner. It used a DEC PDP11/34 minicomputer both to operate the

servo-mechanisms and to acquire and process the images. The Pfizer drug company acquired the prototype from the university, along with rights to manufacture it. Pfizer then began making copies of the prototype, calling it the "200FS" (FS meaning Fast Scan), which were selling as fast as they could make them. This unit produced images in a 256×256 matrix, with much better definition than the EMI-Scanner's 80×80.

Previous studies

A form of tomography can be performed by moving the X-ray source and detector during an exposure. Anatomy at the target level remains sharp, while structures at different levels are blurred. By varying the extent and path of motion, a variety of effects can be obtained, with variable depth of field and different degrees of blurring of "out of plane" structures.[11] :25

Although largely obsolete, conventional tomography is still used in specific situations such as dental imaging (orthopantomography) or in intravenous urography.

Tomosynthesis

Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographic tomography. Although there are some similarities to CT, it is a separate technique. In CT, the source/detector makes a complete 360-degree rotation about the subject obtaining a complete set of data from which images may be reconstructed. In digital tomosynthesis, only a small rotation angle (e.g., 40 degrees) with a small number of discrete exposures (e.g., 10) are used. This incomplete set of data can be digitally processed to yield images similar to conventional tomography with a limited depth of field. However, because the image processing is digital, a series of slices at different depths and with different thicknesses can be reconstructed from the same acquisition, saving both time and radiation exposure.

Because the data acquired is incomplete, tomosynthesis is unable to offer the extremely narrow slice widths that CT offers. However, higher resolution detectors can be used, allowing very-high in-plane resolution, even if the Z-axis resolution is poor. The primary interest in tomosynthesis is in breast imaging, as an extension to mammography, where it may offer better detection rates with little extra increase in radiation exposure.

Reconstruction algorithms for tomosynthesis are significantly different from conventional CT, because the conventional filtered back projection algorithm requires a complete set of data. Iterative algorithms based upon expectation maximization are most commonly used, but are extremely computationally intensive. Some manufacturers have produced practical systems using off-the-shelf GPUs to perform the reconstruction.

Diagnostic use

Since its introduction in the 1970s, CT has become an important tool in medical imaging to supplement X-rays and medical ultrasonography. It has more recently been used for preventive medicine or screening for disease, for example CT colonography for patients with a high risk of colon cancer, or full-motion heart scans for patients with high risk of heart disease. A number of institutions offer full-body scans for the general population. However, this is a controversial practice, given its lack of proven benefit, cost, radiation exposure, and the risk of finding 'incidental' abnormalities that may trigger additional investigations.

Head

CT scanning of the head is typically used to detect infarction, tumours, calcifications, haemorrhage and bone trauma. Of the above, hypodense (dark) structures indicate infarction or tumours, hyperdense (bright) structures indicate calcifications and haemorrhage and bone trauma can be seen as disjunction in bone windows.

Chest

CT can be used for detecting both acute and chronic changes in the lung parenchyma, that is, the internals of the lungs. It is particularly relevant here because normal two dimensional x-rays do not show such defects. A variety of different techniques are used depending on the suspected abnormality. For evaluation of chronic interstitial processes (emphysema, fibrosis, and so forth), thin sections with high spatial frequency reconstructions are used—often scans are performed both in inspiration and expiration. This special technique is called High Resolution CT (HRCT). HRCT is normally done with thin section with skipped areas between the thin sections. Therefore it produces a sampling of the lung and not continuous images. Continuous images are provided in a standard CT of the chest.

For detection of airspace disease (such as pneumonia) or cancer, relatively thick sections and general purpose image reconstruction techniques may be adequate. IV contrast may also be used as it clarifies the anatomy and boundaries of the great vessels and improves assessment of the mediastinum and hilar regions for lymphadenopathy; this is particularly important for accurate assessment of cancer.

CT angiography of the chest is also becoming the primary method for detecting pulmonary embolism (PE) and aortic dissection, and requires accurately timed rapid injections of contrast (Bolus Tracking) and high-speed helical scanners. CT is the standard method of evaluating abnormalities seen on chest X-ray and of following findings of uncertain acute significance. Cardiac CTA is now being used to diagnose coronary artery disease.

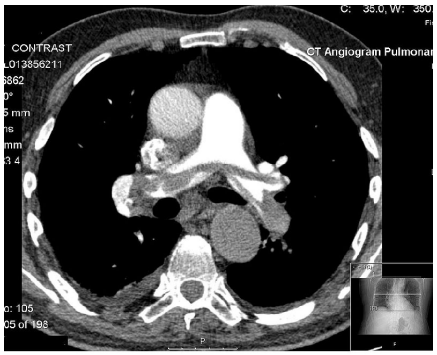
According to the 2007 *New England Journal of Medicine* study, 19.2 million (31%) of the 62 million CTs done every year are for lung CTs.

Pulmonary angiogram

CT pulmonary angiogram (CTPA) is a medical diagnostic test used to diagnose pulmonary embolism (PE). It employs computed tomography to obtain an image of the pulmonary arteries.

It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is a cannula (usually a 20G).

MDCT (multi detector CT) scanners give the optimum resolution and image quality for this test. Images are usually taken on a 0.625 mm slice thickness, although 2 mm is sufficient. 50–100 mls of contrast is given to the patient at a rate of 4 ml/s. The tracker/locator is placed at the level of the pulmonary arteries, which sit roughly at the level of the carina. Images are acquired with the maximum intensity of radio-opaque contrast in the pulmonary arteries. This is done using bolus tracking.



Example of a CTPA, demonstrating a saddle embolus (dark horizontal line) occluding the pulmonary arteries (bright white triangle)

CT machines are now so sophisticated that the test can be done with a patient visit of 5 minutes with an approximate scan time of only 5 seconds or less.

A normal CTPA scan will show the contrast filling the pulmonary vessels, looking bright white. Ideally the aorta should be empty of contrast, to reduce any partial volume artifact which may result in a false positive. Any mass filling defects, such as an embolus, will appear dark in place of the contrast, filling / blocking the space where blood

should be flowing into the lungs.

Cardiac

With the advent of subsecond rotation combined with multi-slice CT (up to 320-slices), high resolution and high speed can be obtained at the same time, allowing excellent imaging of the coronary arteries (cardiac CT angiography). Images with an even higher temporal resolution can be formed using retrospective ECG gating. In this technique, each portion of the heart is imaged more than once while an ECG trace is recorded. The ECG is then used to correlate the CT data with their corresponding phases of cardiac contraction. Once this correlation is complete, all data that were recorded while the heart was in motion (systole) can be ignored and images can be made from the remaining data that happened to be acquired while the heart was at rest (diastole). In this way, individual frames in a cardiac CT investigation have a better temporal resolution than the shortest tube rotation time.

Because the heart is effectively imaged more than once (as described above), cardiac CT angiography results in a relatively high radiation exposure around 12 mSv. Currently, newer acquisition protocols have been developed drastically reducing the xRays radiation exposure, down to 1 milliSievert (cfr. Pavone, Fioranelli, Dowe: Computed Tomography or Coronary Arteries, Springer 2009). For the sake of comparison, a chest X-ray carries a dose of approximately 0.02[12] to 0.2 mSv and natural background radiation exposure is around 0.01 mSv/day. Thus, cardiac CTA is equivalent to approximately 100-600 chest X-rays or over 3 years worth of natural background radiation. Methods are available to decrease this exposure, however, such as prospectively decreasing radiation output based on the concurrently acquired ECG (aka tube current modulation.) This can result in a significant decrease in radiation exposure, at the risk of compromising image quality if there is any arrhythmia during the acquisition. The significance of radiation doses in the diagnostic imaging range has not been proven, although the possibility of inducing an increased cancer risk across a population is a source of significant concern. This potential risk must be weighed against the competing risk of not performing a test and potentially not diagnosing a significant health problem such as coronary artery disease.

It is uncertain whether this modality will replace invasive coronary catheterization. Currently, it appears that the greatest utility of cardiac CT lies in ruling out coronary artery disease rather than ruling it in. This is because the test has a high sensitivity (greater than 90%) and thus a negative test result means that a patient is very unlikely to have coronary artery disease and can be worked up for other causes of their chest symptoms. This is termed a high negative predictive value. A positive result is less conclusive and often will be confirmed (and possibly treated) with subsequent invasive angiography. The positive predictive value of cardiac CTA is estimated at approximately 82% and the negative predictive value is around 93%.

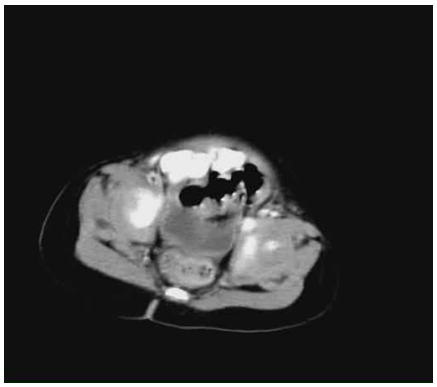
Dual Source CT scanners, introduced in 2005, allow higher temporal resolution by acquiring a full CT slice in only half a rotation, thus reducing motion blurring at high heart rates and potentially allowing for shorter breath-hold time. This is particularly useful for ill patients who have difficulty holding their breath or who are unable to take heart-rate lowering medication.

The speed advantages of 64-slice MSCT have rapidly established it as the minimum standard for newly installed CT scanners intended for cardiac scanning. Manufacturers have developed 320-slice and true 'volumetric' scanners, primarily for their improved cardiac scanning performance.

The latest MSCT scanners acquire images only at 70-80% of the R-R interval (late diastole). This prospective gating can reduce effective dose from 10-15mSv to as little as 1.2mSv in follow-up patients acquiring at 75% of the R-R interval. Effective doses at a centre with well trained staff doing coronary imaging can average less than the doses for conventional coronary angiography.

Abdominal and pelvic

CT is a sensitive method for diagnosis of abdominal diseases. It is used frequently to determine stage of cancer and to follow progress. It is also a useful test to investigate acute abdominal pain (especially of the lower quadrants, whereas ultrasound is the preferred first line investigation for right upper quadrant pain). Renal stones, appendicitis, pancreatitis, diverticulitis, abdominal aortic aneurysm, and bowel obstruction are conditions that are readily diagnosed and assessed with CT. CT is also the first line for detecting solid organ injury after trauma.



CT Scan of 11 cm **Wilms' tumor** of right kidney in 13 month old patient.

Multidetector CT (MDCT) can clearly delineate anatomic structures in the abdomen, which is critical in the diagnosis of internal diaphragmatic and other nonpalpable or unsuspected hernias. MDCT also offers clear detail of the abdominal wall allowing wall hernias to be identified accurately.[13]

Oral and/or rectal contrast may be used depending on the indications for the scan. A dilute (2% w/v) suspension of barium sulfate is most commonly used. The concentrated barium sulfate preparations used for fluoroscopy e.g. barium enema are too dense and cause severe artifacts on CT. Iodinated contrast agents may be used if barium is contraindicated (for example, suspicion of bowel injury). Other agents may be required to optimize the imaging of specific organs, such as rectally administered gas (air or carbon dioxide) or fluid (water) for a colon study, or oral water for a stomach study.

CT has limited application in the evaluation of the *pelvis*. For the female pelvis in particular, ultrasound and MRI are the imaging modalities of choice. Nevertheless, it may be part of abdominal scanning (e.g. for tumors), and has uses in assessing fractures.

CT is also used in osteoporosis studies and research alongside dual energy X-ray absorptiometry (DXA). Both CT and DXA can be used to assess bone mineral density (BMD) which is used to indicate bone strength, however CT results do not correlate exactly with DXA (the gold standard of BMD measurement). CT is far more expensive, and subjects patients to much higher levels of ionizing radiation, so it is used infrequently.

Extremities

CT is often used to image complex fractures, especially ones around joints, because of its ability to reconstruct the area of interest in multiple planes. Fractures, ligamentous injuries and dislocations can easily be recognised with a 0.2 mm resolution. [14] [15]

Advantages and disadvantages

Advantages over traditional radiography

There are several advantages that CT has over traditional 2D medical radiography. First, CT completely eliminates the superimposition of images of structures outside the area of interest. Second, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Finally, data from a single CT imaging procedure consisting of either multiple contiguous or one helical scan can be viewed as images in the axial, coronal, or sagittal planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

CT is regarded as a moderate to high radiation diagnostic technique. While technical advances have improved radiation efficiency, there has been simultaneous pressure to obtain higher-resolution imaging and use more complex

scan techniques, both of which require higher doses of radiation. The improved resolution of CT has permitted the development of new investigations, which may have advantages; compared to conventional angiography for example, CT angiography avoids the invasive insertion of an arterial catheter and guidewire; CT colonography (also known as virtual colonoscopy or VC for short) may be as useful as a barium enema for detection of tumors, but may use a lower radiation dose. CT VC is increasingly being used in the UK as a diagnostic test for bowel cancer and can negate the need for a colonoscopy.

The greatly increased availability of CT, together with its value for an increasing number of conditions, has been responsible for a large rise in popularity. So large has been this rise that, in the most recent comprehensive survey in the United Kingdom, CT scans constituted 7% of all radiologic examinations, but contributed 47% of the total collective dose from medical X-ray examinations in 2000/2001.[16] Increased CT usage has led to an overall rise in the total amount of medical radiation used, despite reductions in other areas. In the United States and Japan for example, there were 26 and 64 CT scanners per 1 million population in 1996. In the U.S., there were about 3 million CT scans performed in 1980, compared to an estimated 62 million scans in 2006.[17]

The radiation dose for a particular study depends on multiple factors: volume scanned, patient build, number and type of scan sequences, and desired resolution and image quality. Additionally, two helical CT scanning parameters that can be adjusted easily and that have a profound effect on radiation dose are tube current and pitch.[18]

Computed tomography (CT) scan has been shown to be more accurate than radiographs in evaluating anterior interbody fusion but may still over-read the extent of fusion.[19]

Safety concerns

The increased use of CT scans has been the greatest in two fields: screening of adults (screening CT of the lung in smokers, virtual colonoscopy, CT cardiac screening and whole-body CT in asymptomatic patients) and CT imaging of children. Shortening of the scanning time to around 1 second, eliminating the strict need for subject to remain still or be sedated, is one of the main reasons for large increase in the pediatric population (especially for the diagnosis of appendicitis).[17] CT scans of children have been estimated to produce non-negligible increases in the probability of lifetime cancer mortality, leading to calls for the use of reduced current settings for CT scans of children.[20] These calculations are based on the assumption of a linear relationship between radiation dose and cancer risk; this claim is controversial, as some but not all evidence shows that smaller radiation doses are not harmful.[17] Estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT in a 1-year-old are 0.18% (abdominal) and 0.07% (head)—an order of magnitude higher than for adults—although those figures still represent a small increase in cancer mortality over the background rate. In the United States, of approximately 600,000 abdominal and head CT examinations annually performed in children under the age of 15 years, a rough estimate is that 500 of these individuals might ultimately die from cancer attributable to the CT radiation.[21] The additional risk is still very low (0.35%) compared to the background risk of dying from cancer (23%).[21] However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5 to 2%. Furthermore, certain conditions can require children to be exposed to multiple CT scans. Again, these calculations can be problematic because the assumptions underlying them could overestimate the risk.[17]

In 2009 a number of studies appeared that further defined the risk of cancer that may be caused by CT scans.[22] One study indicated that radiation by CT scans is often higher and more variable than cited and each of the 19,500 CT scans that are daily performed in the US is equivalent to 30 to 442 chest x-rays in radiation. It has been estimated that CT radiation exposure will result in 29,000 new cancer cases just from the CT scans performed in 2007.[22] The most common cancers caused by CT are thought to be lung cancer, colon cancer and leukemia with younger people and women more at risk. These conclusions, however, are criticized by the American College of Radiology (ACR) that maintains that the life expectancy of CT scanned patients is not that of the general population and that the model of calculating cancer is based on total body radiation exposure and thus faulty.[22]

CT scans can be performed with different settings for lower exposure in children, although these techniques are often not employed. Surveys have suggested that currently, many CT scans are performed unnecessarily. Ultrasound scanning or magnetic resonance imaging are alternatives (for example, in appendicitis or brain imaging) without the risk of radiation exposure. Although CT scans come with an additional risk of cancer (it can be estimated that the radiation exposure from a full body scan is the same as standing 2.4 km away from the WWII atomic bomb blasts in Japan[23] [24]), especially in children, the benefits that stem from their use outweighs the risk in many cases.[21] Studies support informing parents of the risks of pediatric CT scanning.[25]

Typical scan doses

Examination	Typical effective dose (mSv)	(millirem)
Chest X-ray	0.1	10
Head CT	1.5[26]	150
Screening mammography	3[17]	300
Abdomen CT	5.3[26]	530
Chest CT	5.8[26]	580
CT colonography (virtual colonoscopy)	3.6–8.8	360–880
Chest, abdomen and pelvis CT	9.9[26]	990
Cardiac CT angiogram	6.7-13[27]	670–1300
Barium enema	15[17]	1500
Neonatal abdominal CT	20[17]	2000

For purposes of comparison, the average background exposure in the UK is 1-3 mSv per year.

Adverse reactions to contrast agents

Because contrast CT scans rely on intravenously administered contrast agents in order to provide superior image quality, there is a low but non-negligible level of risk associated with the contrast agents themselves. Many patients report nausea and discomfort, including warmth in the crotch which mimics the sensation of wetting oneself. Certain patients may experience severe and potentially life-threatening allergic reactions to the contrast dye.

The contrast agent may also induce kidney damage. The risk of this is increased with patients who have preexisting renal insufficiency, preexisting diabetes, or reduced intravascular volume. In general, if a patient has normal kidney function, then the risks of contrast nephropathy are negligible. Patients with mild kidney impairment are usually advised to ensure full hydration for several hours before and after the injection. For moderate kidney failure, the use of iodinated contrast should be avoided; this may mean using an alternative technique instead of CT, e.g., MRI. Paradoxically, patients with severe renal failure requiring dialysis do not require special precautions, as their kidneys have so little function remaining that any further damage would not be noticeable and the dialysis will remove the contrast agent.

Low-dose CT scan

An important issue within radiology today is how to reduce the radiation dose during CT examinations without compromising the image quality. Generally, higher radiation doses result in higher-resolution images, while lower doses lead to increased image noise and unsharp images. Increased dosage raises the risk of radiation induced cancer — a four-phase abdominal CT gives the same radiation dose as 300 chest x-rays. Several methods exist which can reduce the exposure to ionizing radiation during a CT scan.

1. New software technology can significantly reduce the required radiation dose. The software works as a filter that reduces random noise and enhances structures. In this way, it is possible to get high-quality images and at the same time lower the dose by as much as 30 to 70 percent.
2. Individualize the examination and adjust the radiation dose to the body type and body organ examined. Different body types and organs require different amounts of radiation.
3. Prior to every CT examination, evaluate the appropriateness of the exam whether it is motivated or if another type of examination is more suitable. Higher resolution is not always suitable for any given scenario, such as detection of small pulmonary masses[28]

Computed tomography versus MRI

The basic mathematics of the 2D-Fourier transform in CT reconstruction is very similar to the 2D-FT NMRI, but the computer data processing in CT does differ in detail, as for example in the case of the volume rendering and artifact elimination algorithms that are specific to CT.

Prevalence

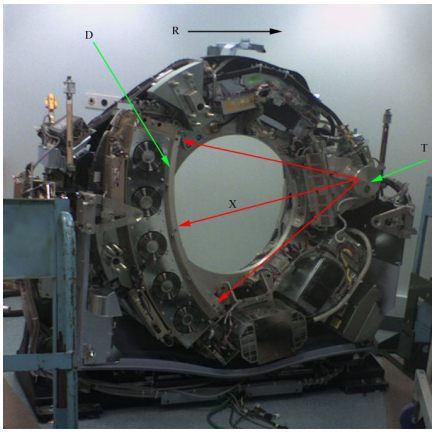
Usage of CT has increased dramatically over the last two decades[29] . An estimated 72 million scans were performed in the United States in 2007.[30] In Calgary Canada 12.1% of people who present to the emergency with an urgent complaint received a CT scan, most commonly either of the head or the abdomen. The percentage who received CT however varied markedly by the emergency physician who saw them from 1.8% to 25%.[31]

Process

X-ray slice data is generated using an X-ray source that rotates around the object; X-ray sensors are positioned on the opposite side of the circle from the X-ray source. The earliest sensors were scintillation detectors, with photomultiplier tubes excited by (typically) cesium iodide crystals. Cesium iodide was replaced during the 1980s by ion chambers containing high pressure Xenon gas. These systems were in turn replaced by scintillation systems based on photo diodes instead of photomultipliers and modern scintillation materials with more desirable characteristics. Many data scans are progressively taken as the object is gradually passed through the gantry.

Newer machines with faster computer systems and newer software strategies can process not only individual cross sections but continuously changing cross sections as the gantry, with the object to be imaged, is slowly and smoothly slid through the X-ray circle. These are called *helical* or *spiral CT* machines. Their computer systems integrate the data of the moving individual slices to generate three dimensional volumetric information (3D-CT scan), in turn viewable from multiple different perspectives on attached CT workstation monitors. This type of data acquisition requires enormous processing power, as the data are arriving in a continuous stream and must be processed in real-time.

In conventional CT machines, an X-ray tube and detector are physically rotated behind a circular shroud (see the image above right); in the electron beam tomography (EBT) the tube is far larger and higher power to support the high temporal resolution. The electron beam is deflected in a hollow funnel-shaped vacuum chamber. X-rays are generated when the beam hits the stationary target. The detector is also stationary. This arrangement can result in very fast scans, but is extremely expensive.



CT scanner with cover removed to show the principle of operation

CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

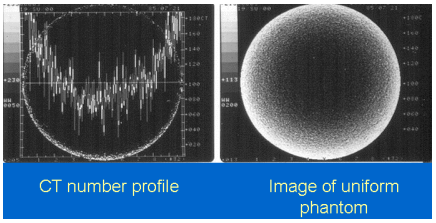
Once the scan data has been acquired, the data must be processed using a form of tomographic reconstruction, which produces a series of cross-sectional images. The most common technique in general use is filtered back projection, which is straight-forward to implement and can be computed rapidly. Mathematically, this method is based on the Radon transform. However, this is not the only technique available: the original EMI scanner solved the tomographic reconstruction problem by linear algebra, but this approach was limited by its high computational complexity, especially given the computer technology available at the time. More recently, manufacturers have developed iterative physical model-based expectation-maximization techniques. These techniques are advantageous because they use an internal model of the scanner's physical properties and of the physical laws of X-ray interactions. By contrast, earlier methods have assumed a perfect scanner and highly simplified physics, which leads to a number of artefacts and reduced resolution - the result is images with improved resolution, reduced noise and fewer artefacts, as well as the ability to greatly reduce the radiation dose in certain circumstances. The disadvantage is a very high computational requirement, which is at the limits of practicality for current scan protocols.

Pixels in an image obtained by CT scanning are displayed in terms of relative radiodensity. The pixel itself is displayed according to the mean attenuation of the tissue(s) that it corresponds to on a scale from +3071 (most attenuating) to -1024 (least attenuating) on the Hounsfield scale. Pixel is a two dimensional unit based on the matrix size and the field of view. When the CT slice thickness is also factored in, the unit is known as a Voxel, which is a three dimensional unit. The phenomenon that one part of the detector cannot differentiate between different tissues is called the *"Partial Volume Effect"*. That means that a big amount of cartilage and a thin layer of compact bone can cause the same attenuation in a voxel as hyperdense cartilage alone. Water has an attenuation of 0 Hounsfield units (HU) while air is -1000 HU, cancellous bone is typically +400 HU, cranial bone can reach 2000 HU or more (os temporale) and can cause artifacts. The attenuation of metallic implants depends on atomic number of the element used: Titanium usually has an amount of +1000 HU, iron steel can completely extinguish the X-ray and is therefore responsible for well-known line-artifacts in computed tomograms. Artifacts are caused by abrupt transitions between low- and high-density materials, which results in data values that exceed the dynamic range of the processing electronics.

Artifacts

Although CT is a relatively accurate test, it is liable to produce artifacts, such as the following:[2] , Chapters 3 and 5

- **Aliasing artifact or streaks**



Example of beam hardening

These appear as dark lines which radiate away from sharp corners. It occurs because it is impossible for the scanner to "sample" or take enough projections of the object, which is usually metallic. It can also occur when an insufficient X-ray tube current is selected, and insufficient penetration of the x-ray occurs. These artifacts are also closely tied to motion during a scan. This type of artifact commonly occurs in head images around the pituitary fossa area.

- **Partial volume effect**

This appears as "blurring" over sharp edges. It is due to the scanner being unable to differentiate between a small amount of high-density material (e.g. bone) and a larger amount of lower density (e.g., cartilage). The processor tries to average out the two densities or structures, and information is lost. This can be partially overcome by scanning using thinner slices.

- **Ring artifact**

Probably the most common mechanical artifact, the image of one or many "rings" appears within an image. This is usually due to a detector fault.

- **Noise artifact**

This appears as graining on the image and is caused by a low signal to noise ratio. This occurs more commonly when a thin slice thickness is used. It can also occur when the power supplied to the X-ray tube is insufficient to penetrate the anatomy.

- **Motion artifact**

This is seen as blurring and/or streaking which is caused by movement of the object being imaged.

- **Windmill**

Streaking appearances can occur when the detectors intersect the reconstruction plane. This can be reduced with filters or a reduction in pitch.

- **Beam hardening**

This can give a "cupped appearance". It occurs when there is more attenuation in the center of the object than around the edge. This is easily corrected by filtration and software.

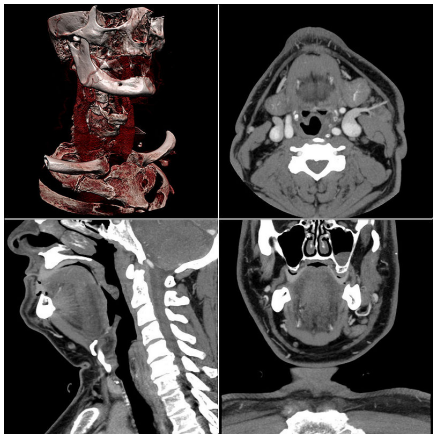
Three-dimensional (3D) image reconstruction

The principle

Because contemporary CT scanners offer isotropic or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by "stacking" the individual slices one on top of the other. The program may then display the volume in an alternative manner.[32]

Multiplanar reconstruction

Multiplanar reconstruction (MPR) is the simplest method of reconstruction. A volume is built by stacking the axial slices. The software then cuts slices through the volume in a different plane (usually orthogonal). Optionally, a special projection method, such as maximum-intensity projection (MIP) or minimum-intensity projection (mIP), can be used to build the reconstructed slices.



Typical screen layout for diagnostic software, showing one 3D and three MPR views

MPR is frequently used for examining the spine. Axial images through the spine will only show one vertebral body at a time and cannot reliably show the intervertebral discs. By reformatting the volume, it becomes much easier to visualise the position of one vertebral body in relation to the others.

Modern software allows reconstruction in non-orthogonal (oblique) planes so that the optimal plane can be chosen to display an anatomical structure. This may be particularly useful for visualising the structure of the bronchi as these do not lie orthogonal to the direction of the scan.

For vascular imaging, curved-plane reconstruction can be performed. This allows bends in a vessel to be "straightened" so that the entire length can be visualised on one image, or a short series of images. Once a vessel has been "straightened" in this way, quantitative measurements of length and cross sectional area can be made, so that surgery or interventional treatment can be planned.

MIP reconstructions enhance areas of high radiodensity, and so are useful for angiographic studies. mIP reconstructions tend to enhance air spaces so are useful for assessing lung structure.

3D rendering techniques

Surface rendering

> A threshold value of radiodensity is set by the operator (e.g. a level that corresponds to bone). From this, a three-dimensional model can be constructed using edge detection image processing algorithms and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

> Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image—e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

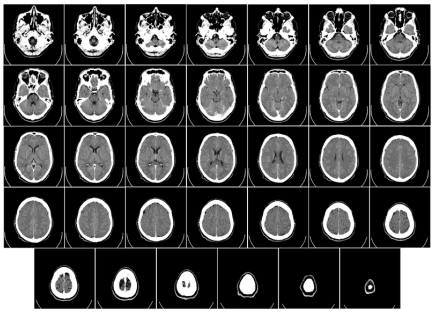
Image segmentation

Where different structures have similar radiodensity, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

Example

Some slices of a cranial CT scan are shown below. The bones are whiter than the surrounding area. (Whiter means higher attenuation.) Note the blood vessels (arrowed) showing brightly due to the injection of an iodine-based contrast agent.

A volume rendering of this volume clearly shows the high density bones.



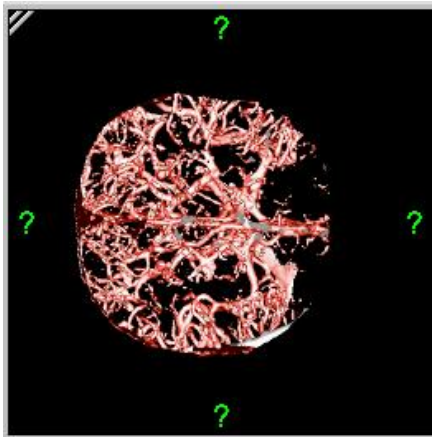
Computed tomography of human brain, from base of the skull to top. Taken with intravenous contrast medium.

After using a segmentation tool to remove the bone, the previously concealed vessels can now be demonstrated.

Bone reconstructed in 3D

Industrial Computed Tomography

Industrial CT Scanning (Industrial Computed Tomography) is a process which utilizes x-ray equipment to produce 3D representations of components both externally and internally. Industrial CT scanning has been utilized in many areas of industry for internal inspection of components. Some of the key uses for CT scanning have been flaw detection, failure analysis, metrology, assembly analysis and reverse engineering applications



Brain vessels reconstructed in 3D after bone has been removed by segmentation

See also

- Virtopsy
- Xenon-enhanced CT scanning
- X-ray microtomography

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External links

- Open-source computed tomography simulator with educational tracing displays (http://ctsim.org)
- idoimaging.com: Free software for viewing CT and other medical imaging files (http://www.idoimaging.com)
- CT Artefacts (http://www.impactscan.org/slides/impactcourse/artefacts/img0.html) by David Platten
- DigiMorph (http://digimorph.org/) A library of 3D imagery based on CT scans of the internal and external structure of living and extinct plants and animals.
- MicroCT and calcified tissues (http://www.med.univ-angers.fr/discipline/lab_histo/page_microCT.htm) A website dedicated to microCT in the microscopic analysis of calcified tissues.
- Free Radiology Resource for Radiologists, Radiographers, and Technical Assistance (http://www.mdct.com.au:)
- Radiation Risk Calculator (http://www.xrayrisk.com) Calculate cancer risk from CT scans and xrays.
- CT scanner video - gantry (http://www.radrounds.com/video/ct-scanner-gantry-full-speed)
- CT in your clinical practice (http://www.ajronline.org/cgi/data/183/3/DC1/1) by Gregory J. Kohs and Joel Legunn.
- Coronary CT angiography by Eugene Lin (http://emedicine.medscape.com/article/1603072-overview)
- CT physics lecture (http://www.radiolopolis.com/index.php/radiology-videos/video-gallery.html?task=viewvideo&video_id=122) excellent video lectures about physics in computed tomography
- Video documentary of patient getting a CT Scan (http://www.rosiescancerfund.com/videos/view/rosies-ct-scan_67.html)

PET Scanning

Positron emission tomography (**PET**) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional or 4-dimensional space (the 4th dimension being time) within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

Image of a typical positron emission tomography (PET) facility

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

PET/CT-System with 16-slice CT; the ceiling mounted device is an injection pump for CT contrast agent

History

The concept of emission and transmission tomography was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.[1] [2]

Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging.[3] Their innovations, including the use of light pipes, and volumetric analysis have been important in the deployment of PET imaging. In 1961, James Robertson and his associates at Brookhaven National Laboratory built the first single-plane PET scan, nicknamed the "head-shrinker." [4]

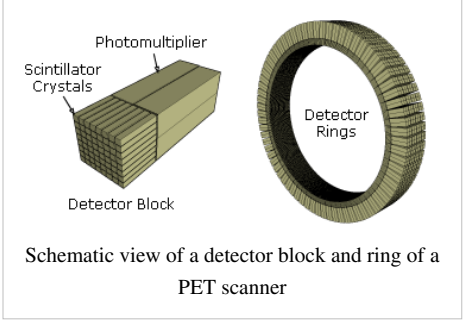
It is interesting that one of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Al Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging.[5] The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968, completed in 1969 and reported in 1972. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were reported in 1970.[6] It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson [7] and Z.H. Cho[8] were the first to propose a ring system which has become the prototype of the current shape of PET.

The PET/CT scanner, attributed to Dr David Townsend and Dr Nutt was named by TIME Magazine as the medical invention of the year in 2000.

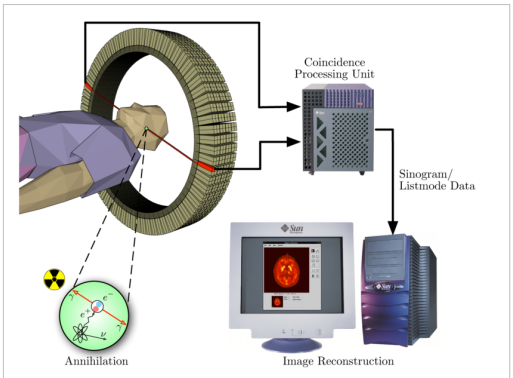
Description

Operation



Schematic view of a detector block and ring of a PET scanner

To conduct the scan, a short-lived radioactive tracer isotope is injected into the living subject (usually into blood circulation). The tracer is chemically incorporated into a biologically active molecule. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the subject is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour. During the scan a record of tissue concentration is made as the tracer decays.



Schema of a PET acquisition process

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope[9]), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron.[10] The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (it would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of a few nanoseconds) are ignored.

Localization of the positron annihilation event

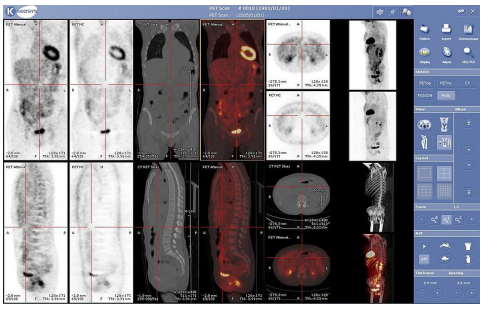
The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the resolving time of the detectors is less than 500 picoseconds rather than about 10 nanoseconds, it is possible to localize the event to a segment of a chord, whose length is determined by the detector timing resolution. As the timing resolution improves, the signal-to-noise ratio (SNR) of the image will improve, requiring fewer events to achieve the same image quality. This technology is not yet common, but it is available on

some new systems.[11]

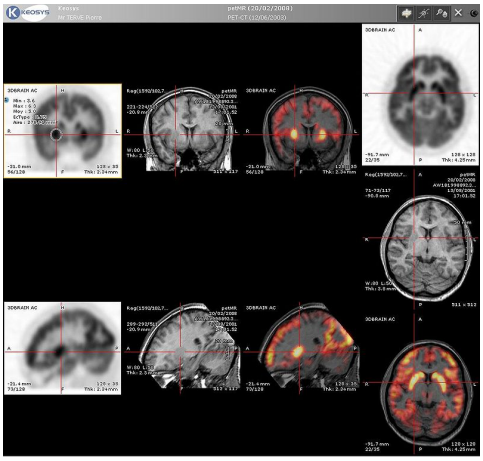
Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult (see Image reconstruction of PET).

Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular tracer has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.



A complete body PET / CT Fusion image



A Brain PET / MRI Fusion image

Combination of PET with CT or MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher anatomical variation, which is more common outside the brain.

At the Jülich Institute of Neurosciences and Biophysics, the world's largest PET/MRI device began operation in April 2009: a 9.4-tesla magnetic resonance tomograph (MRT) combined with a positron emission tomograph (PET). Presently, only the head and brain can be imaged at these high magnetic field strengths.[12]

Radionuclides

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds

applied in research. Presently, however, by far the most commonly used nuclide in clinical PET scanning is fluorine-18 in the form of FDG.

Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough that it can be manufactured commercially at an offsite location.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy,[13] where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with fluorine-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines [14]

Because the half-life of fluorine-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Modern systems with a high time resolution also use a technique (called "Time-of-flight") where they more precisely decide the difference in time between the detection of the two photons and can thus limit the length of the earlier mentioned line to around 10 cm.

Coincidence events can be grouped into projections images, called sinograms. The sinograms are sorted by the angle of each view and tilt, the latter in 3D case images. The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data is much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

While attenuation-corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. The advent of sub-nanosecond timing resolution detectors affords better random coincidence rejection, thus favoring 3D image reconstruction.

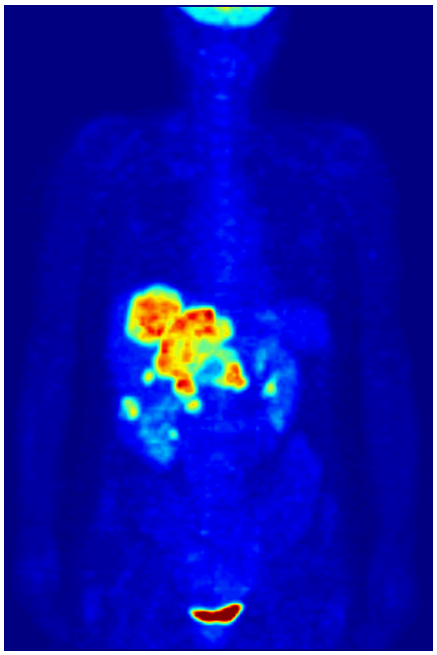
Applications

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET and SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). PET scanning does this using radiolabelled molecular probes that have different rates of uptake depending on the type and function of tissue involved. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.



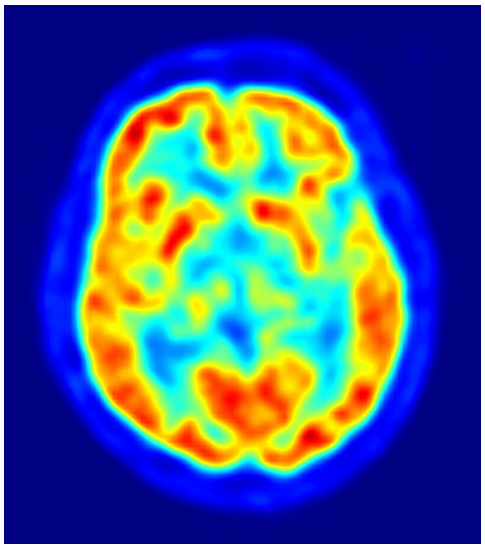
Maximum intensity projection (MIP) of a F-18 FDG wholebody PET acquisition; liver metastases of a colorectal tumor are clearly visible within the abdominal region of the image. Normal physiological isotope uptake is seen in the brain, renal collection systems and bladder. In this animation, it is important to view the subject as rotating clockwise (note liver position).

PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. Oncology: PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's lymphoma, non-Hodgkin lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis—a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health

technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.



PET scan of the human brain.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh compound B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies. [^{11}C]PMP (N-[^{11}C]methylpiperidin-4-yl propionate) is a novel radiopharmaceutical used in PET imaging to determine the activity of the acetylcholinergic neurotransmitter system by acting as a substrate for acetylcholinesterase. Post-mortem examination of AD patients have shown decreased levels of acetylcholinesterase. [^{11}C]PMP is used to map the acetylcholinesterase activity in the brain which could allow for pre-mortem diagnosis of AD and help to monitor AD treatments.[15] Avid Radiopharmaceuticals of Philadelphia has developed a compound called 18F-AV-45 that uses the longer-lasting radionuclide fluorine-18 to detect amyloid plaques using PET scans.[16]

3. Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke [17].
4. Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.
5. Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (mu) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.
6. Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. Such scans are referred to as biodistribution studies. The uptake of the drug, the tissues in which it concentrates, and its

eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. Much more commonly, however, drug occupancy at a purported site of action can be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site. A single radioligand can be used this way to test many potential drug candidates for the same target. A related technique involves scanning with radioligands that compete with an endogenous (naturally occurring) substance at a given receptor to demonstrate that a drug causes the release of the natural substance.

7. PET technology for small animal imaging: A miniature PET tomograph has been constructed that is small enough for a fully conscious and mobile rat to wear on its head while walking around.[18] This RatCAP (Rat Conscious Animal PET) allows animals to be scanned without the confounding effects of anesthesia. PET scanners designed specifically for imaging rodents or small primates are marketed for academic and pharmaceutical research.
8. Musculo-Skeletal Imaging: PET has been shown to be a feasible technique for studying skeletal muscles during exercises like walking.[19] One of the main advantages of using PET is that it can also provide muscle activation data about deeper lying muscles such as the vastus intermedialis and the gluteus minimus, as compared to other muscle studying techniques like Electromyography, which can only be used on superficial muscles (i.e. directly under the skin). A clear disadvantage, however, is that PET provides no timing information about muscle activation, because it has to be measured after the exercise is completed. This is due to the time it takes for FDG to accumulate in the activated muscles.

Pulse Shape Discrimination

The pulse Shape Discrimination (PSD) is a technique used to define which pulse is related to each crystal. Different Techniques were introduced to discriminate between two-types of pulses according to its shape (indeed due to the decay time).

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is not insignificant, usually around 5–7 mSv. However, in modern practice, a combined PET/CT scan is almost always performed, and for PET/CT scanning, the radiation exposure may be substantial - around 23-26 mSv (for a 70 kg person - dose is likely to be higher for higher body weights).[20] When compared to the classification level for radiation workers in the UK, of 6 mSv it can be seen that PET scans need proper justification. This can also be compared to 2.2 mSv average annual background radiation in the UK, 0.02 mSv for a chest x-ray and 6.5 - 8 mSv for a CT scan of the chest, according to the Chest Journal and ICRP.[21] [22] A policy change suggested by the IFALPA member associations in year 1999 mentioned that an aircrew member is likely to receive a radiation dose of 4–9 mSv per year.[23]

See also

- Diffuse optical imaging
- Hot cell (Equipment used to produce the radiopharmaceuticals used in PET)
- Molecular Imaging

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External links

- PET Images (http://rad.usuhs.edu/medpix/master.php3?mode=image_finder&action=search&srchstr=&srch_type=all&labels=&details=2&no_filter=2&plane_id=&capt_id=-4&filter_m=modality&filter_o=&acr_pre=&filter_p=&acr_post=#top) Search MedPix(r)
- Seeing is believing: In vivo functional real-time imaging of transplanted islets using positron emission tomography (PET)(a protocol) (http://www.natureprotocols.com/2006/12/21/seeing_is_believing_in_vivo_fu_1.php), Nature Protocols, from Nature Medicine - 12, 1423 - 1428 (2006).
- The nuclear medicine and molecular medicine podcast (http://nuccast.com) - Podcast
- Positron Emission Particle Tracking (http://www.np.ph.bham.ac.uk/pic/pept.htm) (PEPT) - engineering analysis tool based on PET that is able to track single particles in 3D within mixing systems or fluidised beds. Developed at the University of Birmingham, UK.
- CMS coverage of PET scans (http://www.hematologytimes.com/ht/p_article.do?id=948)
- PET-CT atlas Harvard Medical School (http://www.med.harvard.edu/JPNM/chetan/)

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2D-FT Nuclear Magnetic resonance imaging

(**2D-FT NMRI**), or **Two-dimensional Fourier transform magnetic resonance imaging** (**NMRI**), is primarily a non--invasive imaging technique most commonly used in biomedical research and medical radiology/ nuclear medicine to visualize structures and functions of the living systems and single cells. For example it can provides fairly detailed images of a human body in any selected cross-sectional plane, such as longitudinal, transversal, sagital, etc. NMRI provides much greater contrast especially for the different soft tissues of the body than computed tomography (CT) as its most sensitive option observes the nuclear spin distribution and dynamics of higly mobile molecules that contain the naturally abundant, stable hydrogen isotope ^{1}H as in plasma water molecules, blood, disolved metabolites and fats. This approach makes it most useful in cardiovascular, oncological (cancer), neurological (brain), musculoskeletal, and cartilage imaging. Unlike CT, it uses no ionizing radiation, and also unlike nuclear imaging it does not employ any radioactive isotopes. Some of the first MRI images reported were published in 1973[1] and the first study performed on a human took place on July 3, 1977.[2] Earlier papers were also published by Peter Mansfield in UK (Nobel Laureate in 2007, and R. Damadian in the USA, (together with an approved patent for magnetic imaging). Unpublished `high-resolution' (50 micron resolution) images of other living systems, such as hydrated wheat grains, were obtained and communicated in UK in 1977-1979, and were subsequently confirmed by articles published in *Nature*.

NMRI Principle

Certain nuclei such as ^{1}H nuclei, or `fermions' have spin-1/2, because there are two spin states, referred to as "up" and "down" states. The nuclear magnetic resonance absorption phenomenon occurs when samples containing such nuclear spins are placed in a static magnetic field and a very short radiofrequency pulse is applied with a center, or carrier, frequency matching that of the transition between the up and down states of the spin-1/2 ^{1}H nuclei that were polarized by the static magnetic field.

Modern 3 tesla clinical MRI scanner.

A number of methods have been devised for combining magnetic field gradients and radiofrequency pulsed excitation to obtain an image. Two major maethods involve either 2D -FT or 3D-FT reconstruction from projections, somewhat similar to Computed Tomography, with the exception of the image interpretation that in the former case must include dynamic and relaxation/contrast enhancement information as well. Other schemes involve building the NMR image either point-by-point or line-by-line. Some schemes use instead gradients in the rf field rather than in the static magnetic field. The majority of NMR images routinely obtained are either by the Two-Dimensional Fourier Transform (2D-FT) technique(with slice selection), or by the Three-Dimensional Fourier Transform (3D--FT) techniques that are however much more time consuming at present. 2D-FT NMRI is sometime called in common parlance a "spin-warp". An NMR image corresponds to a spectrum consisting of a number of `spatial frequencies' at different locations in the sample investigated, or in a patient. A two–dimensional Fourier transformation of such a "real" image may be considered as a representation of such "real waves" by a matrix of spatial frequencies known as the k–space. We shall see next in some mathematical detail how the 2D-FT computation works to obtain 2D-FT NMR images.

Two-dimensional Fourier transform imaging

A two-dimensional Fourier transform (2D-FT) is computed numerically or carried out in two stages, both involving `standard', one-dimensional Fourier transforms. However, the second stage Fourier transform is not the inverse Fourier transform (which would result in the original function that was transformed at the first stage), but a Fourier transform in a second variable-- which is `shifted' in value-- relative to that involved in the result of the first Fourier transform. Such 2D-FT analysis is a very powerful method for three-dimensional reconstruction of polymer and biopolymer structures by two-dimensional Nuclear Magnetic Resonance (Kurt Wutrich 1986: 2D-FT NMR of solutions [3]) for molecular weights (Mw) of the dissolved polymers up to about 50,000 Mw. For larger biopolymers or polymers, more complex methods have been developed to obtain the desired resolution needed for the 3D-reconstruction of higher molecular structures, e.g. for 900,000 Mw, methods that can also be utilized *in vivo*. The 2D-FT method is also widely utilized in optical spectroscopy, such as *2D-FT NIR hyperspectral imaging*, or in MRI imaging for research and clinical, diagnostic applications in Medicine. A more precise mathematical definition of the `double' Fourier transform involved is specified next, and a precise example follows the definition. A *2D-FT, or two-dimensional Fourier transform*, is a standard Fourier transformation of a function of two variables, $f(x_1, x_2)$, carried first in the first variable x_1, followed by the Fourier transform in the second variable $x_2$of the resulting function $F(s_1, x_2)$.

Example 1

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals : $s(t_1, t_2)$yielding a real 2D-FT NMR `spectrum' (collection of 1D FT-NMR spectra) represented by a matrix **S** whose elements are

$$S(\nu_1, \nu_2) = \mathbf{Re} \int \int cos(\nu_1 t_1) exp^{(-i\nu_2 t_2)} s(t_1, t_2) dt_1 dt_2$$

where : $\nu_1$and : $\nu_2$denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the \emph{covariance matrix} is calculated in the frequency domain according to the following equation

$$C(\nu_2', \nu_2) = S^T S = \sum_{\nu^1} [S(\nu_1, \nu_2') S(\nu_1, \nu_2)], \text{with : } \nu_2, \nu_2' \text{taking all possible single-quantum}$$

frequency values and with the summation carried out over all discrete, double quantum frequencies : ν_1.

Example 2

2D-FT STEM Images [4] (obtained at Cornell University) of electron distributions in a high-temperature cuprate superconductor `paracrystal' reveal both the domains (or `location') and the local symmetry of the 'pseudo-gap' in the electron-pair correlation band responsible for the high--temperature superconductivity effect (maybe a possible, next Nobel if and only if the mathematical physics treatment is also developed to include also such results). So far there have been three Nobel prizes awarded for 2D-FT NMR/MRI during 1992-2003, and an additional, earlier Nobel prize for 2D-FT of X-ray data (`CAT scans'); recently the advanced possibilities of 2D-FT techniques in Chemistry, Physiology and Medicine [5] received very significant recognition.

Brief explanation of NMRI Diagnostic Uses in Pathology

As an example, a diseased tissue, such as that inside tumors, can be detected because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates. By changing the pulse delays in the RF pulse sequence employed, and or the pulse sequence itself one may obtain a `relaxation-based contrast' between different types of body tissue, such as normal vs. diseased tissue cells for example. Excluded from such diagnostic observations by NMRI are all patients with some metal implants, cochlear implants, and all cardiac pacemaker patients who cannot undergo any NMRI scan because of the very intense magnetic and rf fields employed in NMRI. It is conceivable that future developments may also include along with the NMRI diagnostic treatments with special techniques involving applied magnetic fields and very high frequency RF. Already, surgery with special tools is being experimented on in the presence of NMR imaging of subjects.Thus, NMRI is used to image almost every part of the body, and is especiallyuseful in neurological conditions, disorders of the muscles and joints, for evaluating tumors, such as in lung or skin cancers, abnormalities in the heart (especially in children with hereditary disorders), blood vessels, CAD and atherosclerosis.

See also

- Earth's field NMR (EFNMR)
- Magnetic resonance microscopy
- Nuclear magnetic resonance (NMR)
- Medical imaging
- Magnetic resonance elastography
- Relaxation
- Robinson oscillator

Footnotes

[1] Lauterbur, P.C., Nobel Laureate in 2003 (1973). "Image Formation by Induced Local Interactions: Examples of Employing Nuclear Magnetic Resonance". *Nature* **242**: 190–1. doi:10.1038/242190a0.

[2] [http://www.howstuffworks.com/mri.htm/printable Howstuffworks "How MRI Works"

[3] http://en.wikipedia.org/wiki/Nuclear_magnetic_resonance#Nuclear_spin_and_magnets

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[5] http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf

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- 2D-FT NMRI Instrument example: A JPG color image of a 2D-FT NMR Imaging `monster' Instrument (http://upload.wikimedia.org/wikipedia/en/b/bf/HWB-NMRv900.jpg).
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PDF of 2D-FT Imaging Applications to MRI in Medical Research (http://www.wpi.edu/Pubs/ETD/Available/etd-081707-080430/unrestricted/dbennett.pdf).

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- Haacke, E Mark; Brown, Robert F; Thompson, Michael; Venkatesan, Ramesh (1999). *Magnetic resonance imaging: physical principles and sequence design*. New York: J. Wiley & Sons. ISBN 0-471-35128-8.

External links

- 3D Animation Movie about MRI Exam (http://www.patiencys.com/MRI/)
- Interactive Flash Animation on MRI (http://www.e-mri.org) - *Online Magnetic Resonance Imaging physics and technique course*
- International Society for Magnetic Resonance in Medicine (http://www.ismrm.org)
- Danger of objects flying into the scanner (http://www.simplyphysics.com/flying_objects.html)

See also

- Earth's field NMR (EFNMR)
- Medical imaging
- Magnetic resonance microscopy
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Relaxation
- Robinson oscillator
- Rabi cycle

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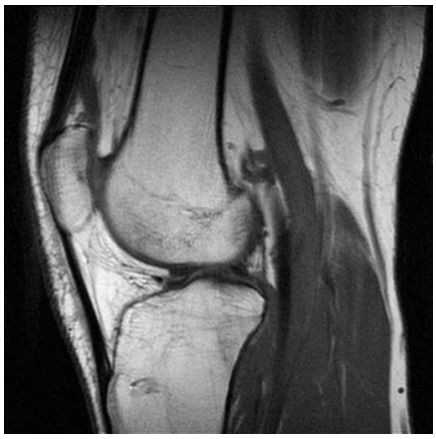
Magnetic resonance imaging

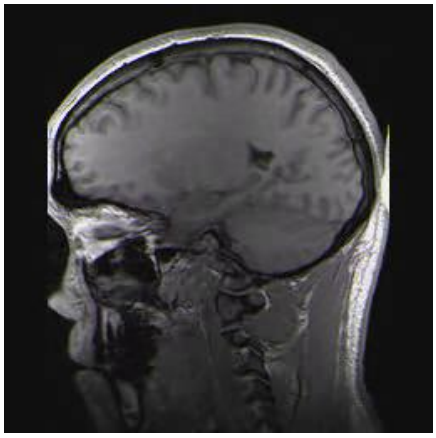
Magnetic resonance imaging (**MRI**), **nuclear magnetic resonance imaging** (**NMRI**), or **magnetic resonance tomography** (**MRT**) is a medical imaging technique used in radiology to visualize detailed internal structures. The good contrast it provides between the different soft tissues of the body make it especially useful in brain, muscles, heart, and cancer compared with other medical imaging techniques such as computed tomography (CT) or X-rays.



Sagittal MR image of the knee

Unlike CT scans or traditional X-rays MRI uses no ionizing radiation. Instead it uses a powerful magnetic field to align the magnetization of some atoms in the body, then uses radio frequency fields to systematically alter the alignment of this magnetization. This causes the nuclei to produce a rotating magnetic field detectable by the scanner—and this information is recorded to construct an image of the scanned area of the body.[1] :36

Magnetic resonance imaging is a relatively new technology. The first MR image was published in 1973[2] [3] and the first cross-sectional image of a living mouse was published in January 1974.[4] The first studies performed on humans were published in 1977.[5] [6] By comparison, the first human X-ray image was taken in 1895.



Para-sagittal MRI of the head, with aliasing artifacts (nose and forehead appear at the back of the head)

How MRI works

The body is largely composed of water molecules. Each water molecule has two hydrogen nuclei or protons. When a person goes inside the powerful magnetic field of the scanner, the magnetic moments of some of these protons changes, and aligns with the direction of the field.

In an MRI machine a radio frequency transmitter is briefly turned on, producing an electromagnetic field. The photons of this field have just the right energy, known as the resonance frequency, to flip the spin of the aligned protons in the body. As the intensity and duration of application of the field increase, more aligned spins are affected. After the field is turned off, the protons decay to the original spin-down state and the difference in energy between the two states is released as a photon. It is these photons that produce the electromagnetic signal that the scanner detects. The frequency the protons resonate at depends on the strength of the magnetic field. As a result of conservation of energy, this also dictates the frequency of the released photons. The photons released when the field is removed have an energy — and therefore a frequency — due to the amount of energy the protons absorbed while the field was active.

It is this relationship between field-strength and frequency that allows the use of nuclear magnetic resonance for imaging. Additional magnetic fields are applied during the scan to make the magnetic field strength depend on the position within the patient, in turn making the frequency of the released photons dependent on position in a predictable manner. Position information can then be recovered from the resulting signal by the use of a Fourier transform. These fields are created by passing electric currents through specially-wound solenoids, known as gradient coils. Since these coils are within the bore of the scanner, there are large forces between them and the main field coils, producing most of the noise that is heard during operation. Without efforts to dampen this noise, it can

approach 130 decibels (dB) with strong fields [7] (see also the subsection on acoustic noise).

An image can be constructed because the protons in different tissues return to their equilibrium state at different rates, which is a difference that can be detected. Five different tissue variables — spin density, T_1 and T_2 relaxation times and flow and spectral shifts can be used to construct images.[8] By changing the parameters on the scanner, this effect is used to create contrast between different types of body tissue or between other properties, as in fMRI and diffusion MRI.

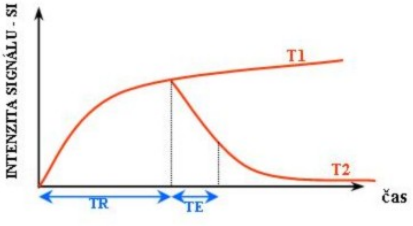
Contrast agents may be injected intravenously to enhance the appearance of blood vessels, tumors or inflammation. Contrast agents may also be directly injected into a joint in the case of arthrograms, MRI images of joints. Unlike CT, MRI uses no ionizing radiation and is generally a very safe procedure. Nonetheless the strong magnetic fields and radio pulses can affect metal implants, including cochlear implants and cardiac pacemakers. In the case of cochlear implants, the US FDA has approved some implants for MRI compatibility. In the case of cardiac pacemakers, the results can sometimes be lethal,[9] so patients with such implants are generally not eligible for MRI.

MRI is used to image every part of the body, and is particularly useful for tissues with many hydrogen nuclei and little density contrast, such as the brain, muscle, connective tissue and most tumors.

Applications

In clinical practice, MRI is used to distinguish pathologic tissue (such as a brain tumor) from normal tissue. One advantage of an MRI scan is that it is harmless to the patient. It uses strong magnetic fields and non-ionizing radiation in the radio frequency range, unlike CT scans and traditional X-rays, which both use ionizing radiation.

While CT provides good spatial resolution (the ability to distinguish two separate structures an arbitrarily small distance from each other), MRI provides comparable resolution with far better contrast resolution (the ability to distinguish the differences between two arbitrarily similar but not identical tissues). The basis of this ability is the complex library of *pulse sequences* that the modern medical MRI scanner includes, each of which is optimized to provide *image contrast* based on the chemical sensitivity of MRI.



Effects of TR, TE, T1 and T2 on MR signal.

For example, with particular values of the *echo time* (T_E) and the *repetition time* (T_R), which are basic parameters of image acquisition, a sequence takes on the property of T_2-weighting. On a T_2-weighted scan, water- and fluid-containing tissues are bright (most modern T_2 sequences are actually *fast* T_2 sequences) and fat-containing tissues are dark. The reverse is true for T_1-weighted images. Damaged tissue tends to develop edema, which makes a T_2-weighted sequence sensitive for pathology, and generally able to distinguish pathologic tissue from normal tissue. With the addition of an additional radio frequency pulse and additional manipulation of the magnetic gradients, a T_2-weighted sequence can be converted to a **FLAIR** sequence, in which free water is now dark, but edematous tissues remain bright. This sequence in particular is currently the most sensitive way to evaluate the brain for demyelinating diseases, such as multiple sclerosis.

The typical MRI examination consists of 5–20 sequences, each of which are chosen to provide a particular type of information about the subject tissues. This information is then synthesized by the interpreting physician.

Basic MRI scans

T_1-weighted MRI

T_1-weighted scans are a standard basic scan, in particular differentiating fat from water - with water darker and fat brighter[10] use a gradient echo (GRE) sequence, with short T_E and short T_R. This is one of the basic types of MR contrast and is a commonly run clinical scan. The T_1 weighting can be increased (improving contrast) with the use of an inversion pulse as in an MP-RAGE sequence. Due to the short repetition time (T_R) this scan can be run very fast allowing the collection of high resolution 3D datasets. A T_1 reducing gadolinium contrast agent is also commonly used, with a T_1 scan being collected before and after administration of contrast agent to compare the difference. In the brain T_1-weighted scans provide good gray matter/white matter contrast; in other words, T_1-weighted images highlight fat deposition.

T_2-weighted MRI

T_2-weighted scans are another basic type. Like the T1-weighted scan, fat is differentiated from water - but in this case fat shows darker, and water lighter. They are therefore particularly well suited to imaging edema.[11] On brain scans cerebral white matter (fat containing) therefore shows as darker than the grey matter. T_2-weighted scans use a spin echo (SE) sequence, with long T_E and long T_R. They have long been the clinical workhorse as the spin echo sequence is less susceptible to inhomogeneities in the magnetic field.

T_2^*-weighted MRI

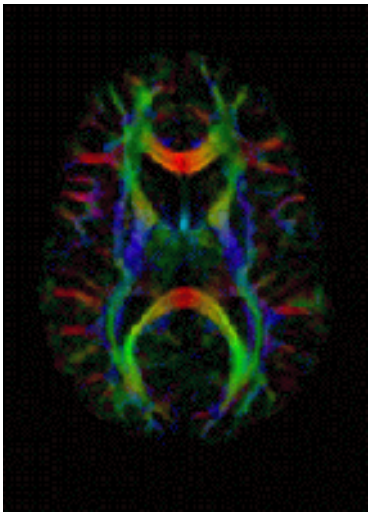
T_2^* (pronounced "T 2 star") weighted scans use a gradient echo (GRE) sequence, with long T_E and long T_R. The gradient echo sequence used does not have the extra refocusing pulse used in spin echo so it is subject to additional losses above the normal T_2 decay (referred to as T_2'), these taken together are called T_2^*. This also makes it more prone to susceptibility losses at air/tissue boundaries, but can increase contrast for certain types of tissue, such as venous blood.

Spin density weighted MRI

Spin density, also called proton density, weighted scans try to have no contrast from either T_2 or T_1 decay, the only signal change coming from differences in the amount of available spins (hydrogen nuclei in water). It uses a spin echo or sometimes a gradient echo sequence, with short T_E and long T_R.

Specialized MRI scans

Diffusion MRI



DTI image

Diffusion MRI measures the diffusion of water molecules in biological tissues.[12] In an isotropic medium (inside a glass of water for example) water molecules naturally move randomly according to turbulence and Brownian motion. In biological tissues however, where the Reynold's number is low enough for flows to be laminar, the diffusion may be anisotropic. For example a molecule inside the axon of a neuron has a low probability of crossing the myelin membrane. Therefore the molecule moves principally along the axis of the neural fiber. If we know that molecules in a particular voxel diffuse principally in one direction we can make the assumption that the majority of the fibers in this area are going parallel to that direction.

The recent development of diffusion tensor imaging (DTI)[3] enables diffusion to be measured in multiple directions and the fractional anisotropy in each direction to be calculated for each voxel. This enables researchers to make brain maps of fiber directions to examine the connectivity of different regions in the brain (using tractography) or to examine areas of neural degeneration and demyelination in diseases like Multiple Sclerosis.

Another application of diffusion MRI is diffusion-weighted imaging (DWI). Following an ischemic stroke, DWI is highly sensitive to the changes occurring in the lesion.[13] It is speculated that increases in restriction (barriers) to water diffusion, as a result of cytotoxic edema (cellular swelling), is responsible for the increase in signal on a DWI scan. The DWI enhancement appears within 5–10 minutes of the onset of stroke symptoms (as compared with computed tomography, which often does not detect changes of acute infarct for up to 4–6 hours) and remains for up to two weeks. Coupled with imaging of cerebral perfusion, researchers can highlight regions of "perfusion/diffusion mismatch" that may indicate regions capable of salvage by reperfusion therapy.

Like many other specialized applications, this technique is usually coupled with a fast image acquisition sequence, such as echo planar imaging sequence.

Magnetization Transfer MRI

Magnetization transfer (MT) refers to the transfer of longitudinal magnetization from free water protons to hydration water protons in NMR and MRI.

In magnetic resonance imaging of molecular solutions, such as protein solutions, two types of water molecules, free (bulk) and hydration (bound), are found. Free water protons have faster average rotational frequency and hence less fixed water molecules that may cause local field inhomogeneity. Because of this uniformity, most free water protons have resonance frequency lying narrowly around the normal proton resonance frequency of 63 MHz (at 1.5 teslas). This also results in slower transverse magnetization dephasing and hence longer T_2. Conversely, hydration water molecules are slowed down by interaction with solute molecules and hence create field inhomogeneities that lead to wider resonance frequency spectrum.

Fluid attenuated inversion recovery (FLAIR)

Fluid Attenuated Inversion Recovery (FLAIR)[14] is an inversion-recovery pulse sequence used to null signal from fluids. For example, it can be used in brain imaging to suppress cerebrospinal fluid (CSF) so as to bring out the periventricular hyperintense lesions, such as multiple sclerosis (MS) plaques. By carefully choosing the inversion time TI (the time between the inversion and excitation pulses), the signal from any particular tissue can be suppressed.

Magnetic resonance angiography

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) generates pictures of the arteries to evaluate them for stenosis (abnormal narrowing) or aneurysms (vessel wall dilatations, at risk of rupture). MRA is often used to evaluate the arteries of the neck and brain, the thoracic and abdominal aorta, the renal arteries, and the legs (called a "run-off"). A variety of techniques can be used to generate the pictures, such as administration of a paramagnetic contrast agent (gadolinium) or using a technique known as "flow-related enhancement" (e.g. 2D and 3D time-of-flight sequences), where most of the signal on an image is due to blood that recently moved into that plane, see also FLASH MRI. Techniques involving phase accumulation (known as phase contrast angiography) can also be used to generate flow velocity maps easily and accurately. Magnetic resonance venography (MRV) is a similar procedure that is used to image veins. In this method, the tissue is now excited inferiorly, while signal is gathered in the plane immediately superior to the excitation plane—thus imaging the venous blood that recently moved from the excited plane.[15]

Magnetic resonance gated intracranial CSF dynamics (MR-GILD)

Magnetic resonance gated intracranial cerebrospinal fluid (CSF) or liquor dynamics (MR-GILD) technique is an MR sequence based on bipolar gradient pulse used to demonstrate CSF pulsatile flow in ventricles, cisterns, aqueduct of Sylvius and entire intracranial CSF pathway. It is a method for analyzing CSF circulatory system dynamics in patients with CSF obstructive lesions such as normal pressure hydrocephalus. It also allows visualization of both arterial and venous pulsatile blood flow in vessels without use of contrast agents.[16] [17]

Diastolic time data acquisition (DTDA).	Systolic time data acquisition (STDA).
	

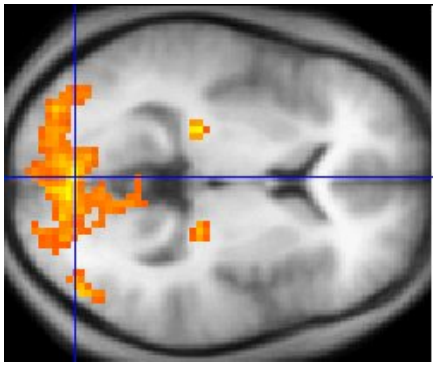
Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is used to measure the levels of different metabolites in body tissues. The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain,[18] and to provide information on tumor metabolism.[19]

Magnetic resonance spectroscopic imaging (MRSI) combines both spectroscopic and imaging methods to produce spatially localized spectra from within the sample or patient. The spatial resolution is much lower (limited by the available SNR), but the spectra in each voxel contains information about many metabolites. Because the available signal is used to encode spatial and spectral information, MRSI requires high SNR achievable only at higher field strengths (3 T and above).

Functional MRI

Functional MRI (fMRI) measures signal changes in the brain that are due to changing neural activity. The brain is scanned at low resolution but at a rapid rate (typically once every 2–3 seconds). Increases in neural activity cause changes in the MR signal via T_2^* changes;[20] this mechanism is referred to as the BOLD (blood-oxygen-level dependent) effect. Increased neural activity causes an increased demand for oxygen, and the vascular system actually overcompensates for this, increasing the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Because deoxygenated hemoglobin attenuates the MR signal, the vascular response leads to a signal increase that is related to the neural activity. The precise nature of the relationship between neural activity and the BOLD signal is a subject of current research. The BOLD effect also allows for the generation of high resolution 3D maps of the venous vasculature within neural tissue.



A fMRI scan showing regions of activation in orange, including the primary visual cortex (V1, BA17).

While BOLD signal is the most common method employed for neuroscience studies in human subjects, the flexible nature of MR imaging provides means to sensitize the signal to other aspects of the blood supply. Alternative techniques employ arterial spin labeling (ASL) or weight the MRI signal by cerebral blood flow (CBF) and cerebral blood volume (CBV). The CBV method requires injection of a class of MRI contrast agents that are now in human clinical trials. Because this method has been shown to be far more sensitive than the BOLD technique in preclinical studies, it may potentially expand the role of fMRI in clinical applications. The CBF method provides more quantitative information than the BOLD signal, albeit at a significant loss of detection sensitivity.

Real-time MRI

Real-time MRI refers to the continuous monitoring (“filming”) of moving objects in real time. While many different strategies have been developed over the past two decades, a recent development reported a real-time MRI technique based on radial FLASH that yields a temporal resolution of 20 to 30 milliseconds for images with an in-plane resolution of 1.5 to 2.0 mm. The new method promises to add important information about diseases of the joints and the heart. In many cases MRI examinations may become easier and more comfortable for patients.

Interventional MRI

The lack of harmful effects on the patient and the operator make MRI well-suited for "interventional radiology", where the images produced by a MRI scanner are used to guide minimally invasive procedures. Of course, such procedures must be done without *any* ferromagnetic instruments.

A specialized growing subset of interventional MRI is that of intraoperative MRI in which the MRI is used in the surgical process. Some specialized MRI systems have been developed that allow imaging concurrent with the surgical procedure. More typical, however, is that the surgical procedure is temporarily interrupted so that MR images can be acquired to verify the success of the procedure or guide subsequent surgical work.

Radiation therapy simulation

Because of MRI's superior imaging of soft tissues, it is now being utilized to specifically locate tumors within the body in preparation for radiation therapy treatments. For therapy simulation, a patient is placed in specific, reproducible, body position and scanned. The MRI system then computes the precise location, shape and orientation of the tumor mass, correcting for any spatial distortion inherent in the system. The patient is then marked or tattooed with points that, when combined with the specific body position, permits precise triangulation for radiation therapy.

Current density imaging

Current density imaging (CDI) endeavors to use the phase information from images to reconstruct current densities within a subject. Current density imaging works because electrical currents generate magnetic fields, which in turn affect the phase of the magnetic dipoles during an imaging sequence. To date no successful CDI has been performed using biological currents, but several studies have been published that involve currents applied through a pair of electrodes.

Magnetic resonance guided focused ultrasound

In MRgFUS therapy, ultrasound beams are focused on a tissue—guided and controlled using MR thermal imaging—and due to the significant energy deposition at the focus, temperature within the tissue rises to more than 65 °C (150 °F), completely destroying it. This technology can achieve precise ablation of diseased tissue. MR imaging provides a three-dimensional view of the target tissue, allowing for precise focusing of ultrasound energy. The MR imaging provides quantitative, real-time, thermal images of the treated area. This allows the physician to ensure that the temperature generated during each cycle of ultrasound energy is sufficient to cause thermal ablation within the desired tissue and if not, to adapt the parameters to ensure effective treatment.

Multinuclear imaging

Hydrogen is the most frequently imaged nucleus in MRI because it is present in biological tissues in great abundance. However, any nucleus with a net nuclear spin could potentially be imaged with MRI. Such nuclei include helium-3, carbon-13, fluorine-19, oxygen-17, sodium-23, phosphorus-31 and xenon-129. ^{23}Na, ^{31}P and ^{17}O are naturally abundant in the body, so can be imaged directly. Gaseous isotopes such as ^{3}He or ^{129}Xe must be hyperpolarized and then inhaled as their nuclear density is too low to yield a useful signal under normal conditions. ^{17}O, ^{13}C and ^{19}F can be administered in sufficient quantities in liquid form (e.g. ^{17}O-water, ^{13}C-glucose solutions or perfluorocarbons) that hyperpolarization is not a necessity.

Multinuclear imaging is primarily a research technique at present. However, potential applications include functional imaging and imaging of organs poorly seen on ^{1}H MRI (e.g. lungs and bones) or as alternative contrast agents. Inhaled hyperpolarized ^{3}He can be used to image the distribution of air spaces within the lungs. Injectable solutions containing ^{13}C or stabilized bubbles of hyperpolarized ^{129}Xe have been studied as contrast agents for angiography and perfusion imaging. ^{31}P can potentially provide information on bone density and structure, as well as functional imaging of the brain.

Susceptibility weighted imaging (SWI)

Susceptibility weighted imaging (SWI), is a new type of contrast in MRI different from spin density, T_1, or T_2 imaging. This method exploits the susceptibility differences between tissues and uses a fully velocity compensated, three dimensional, RF spoiled, high-resolution, 3D gradient echo scan. This special data acquisition and image processing produces an enhanced contrast magnitude image very sensitive to venous blood, hemorrhage and iron storage. It is used to enhance the detection and diagnosis of tumors, vascular and neurovascular diseases (stroke and hemorrhage, multiple sclerosis, Alzheimer's), and also detects traumatic brain injuries that may not be diagnosed using other methods[21]

Other specialized MRI techniques

field of research and new methods and variants are often published when they are able to get better results in specific fields. Examples of these recent improvements are T_2^*-weighted turbo spin-echo (T_2 TSE MRI), double inversion recovery MRI (DIR-MRI) or phase-sensitive inversion recovery MRI (PSIR-MRI), all of them able to improve imaging of the brain lesions.[22] [23] Another example is MP-RAGE (magnetization-prepared rapid acquisition with gradient echo),[24] which improves images of multiple sclerosis cortical lesions.[25]

Portable instruments

Portable magnetic resonance instruments are available for use in education and field research. Using the principles of Earth's field NMR, they have no powerful polarizing magnet, so that such instruments can be small and inexpensive. Some can be used for both EFNMR spectroscopy and MRI imaging.[26] The low strength of the Earth's field results in poor signal to noise ratios, requiring long scan times to capture spectroscopic data or build up MRI images.

Research with atomic magnetometers have discussed the possibility for cheap and portable MRI instruments without the large magnet.[27] [28]

MRI versus CT

A computed tomography (CT) scanner uses X-rays, a type of ionizing radiation, to acquire its images, making it a good tool for examining tissue composed of elements of a higher atomic number than the tissue surrounding them, such as bone and calcifications (calcium based) within the body (carbon based flesh), or of structures (vessels, bowel). MRI, on the other hand, uses non-ionizing radio frequency (RF) signals to acquire its images and is best suited for non-calcified tissue, though MR images can also be acquired from bones and teeth[29] as well as fossils.[30]

CT may be enhanced by use of contrast agents containing elements of a higher atomic number than the surrounding flesh such as iodine or barium. Contrast agents for MRI have paramagnetic properties, e.g., gadolinium and manganese.

Both CT and MRI scanners are able to generate multiple two-dimensional cross-sections (slices) of tissue and three-dimensional reconstructions. Unlike CT, which uses only X-ray attenuation to generate image contrast, MRI has a long list of properties that may be used to generate image contrast. By variation of scanning parameters, tissue contrast can be altered and enhanced in various ways to detect different features. (See Applications above.)

MRI can generate cross-sectional images in any plane (including oblique planes). In the past, CT was limited to acquiring images in the axial (or near axial) plane. The scans used to be called Computed *Axial* Tomography scans (CAT scans). However, the development of multi-detector CT scanners with near-isotropic resolution, allows the CT scanner to produce data that can be retrospectively reconstructed in any plane with minimal loss of image quality.

For purposes of tumor detection and identification in the brain, MRI is generally superior.[31] [32] [33] However, in the case of solid tumors of the abdomen and chest, CT is often preferred due to less motion artifact. Furthermore, CT usually is more widely available, faster, less expensive, and may be less likely to require the person to be sedated or anesthetized.

MRI is also best suited for cases when a patient is to undergo the exam several times successively in the short term, because, unlike CT, it does not expose the patient to the hazards of ionizing radiation.

Economics of MRI

MRI equipment is expensive. 1.5 tesla scanners often cost between $1 million and $1.5 million USD. 3.0 tesla scanners often cost between $2 million and $2.3 million USD. Construction of MRI suites can cost up to $500,000 USD, or more, depending on project scope.


Looking through an MRI scanner.

MRI scanners have been significant sources of revenue for healthcare providers in the US. This is because of favorable reimbursement rates from insurers and federal government programs. Insurance reimbursement is provided in two components, an equipment charge for the actual performance of the MRI scan and professional charge for the radiologist's review of the images and/or data. In the US Northeast, an equipment charge might be $3,500 and a professional charge might be $350 [34] although the actual fees received by the equipment owner and interpreting physician are often significantly less and depend on the rates negotiated with insurance companies or determined by governmental action as in the Medicare Fee Schedule. For example, an orthopedic surgery group in Illinois billed a charge of $1,116 for a knee MRI in 2007 but the Medicare reimbursement in 2007 was only $470.91.[35] Many insurance companies require preapproval of an MRI procedure as a condition for coverage.

In the US, the Deficit Reduction Act of 2007 significantly reduced reimbursement rates paid by federal insurance programs for the equipment component of many scans, shifting the economic landscape. Many private insurers have followed suit.

Safety

A number of features of MRI scanning can give rise to risks.

These include:

- Powerful magnetic fields
- Cryogenic liquids
- Noise
- Claustrophobia

In addition, in cases where MRI contrast agents are used, these also typically have associated risks.

Magnetic field

Most forms of medical or biostimulation implants are generally considered contraindications for MRI scanning. These include pacemakers, vagus nerve stimulators, implantable cardioverter-defibrillators, loop recorders, insulin pumps, cochlear implants, deep brain stimulators. Patients are therefore always asked for complete information about all implants before entering the room for an MRI scan. Several deaths have been reported in patients with pacemakers who have undergone MRI scanning without appropriate precautions. To reduce such risks, implants are increasingly being developed to make them able to be safely scanned[36] , and specialized protocols have been developed to permit the safe scanning of selected implants and pacing devices.

Ferromagnetic foreign bodies such as shell fragments, or metallic implants such as surgical prostheses and aneurysm clips are also potential risks. Interaction of the magnetic and radio frequency fields with such objects can lead to trauma due to movement of the object in the magnetic field or thermal injury from radio-frequency induction heating

of the object.

Titanium and its alloys are safe from movement from the magnetic field.

In the United States a classification system for implants and ancillary clinical devices has been developed by ASTM International and is now the standard supported by the US Food and Drug Administration:

MR-Safe — The device or implant is completely non-magnetic, non-electrically conductive, and non-RF reactive, eliminating all of the primary potential threats during an MRI procedure.

MR Safe sign

MR-Conditional — A device or implant that may contain magnetic, electrically conductive or RF-reactive components that is safe for operations in proximity to the MRI, provided the conditions for safe operation are defined and observed (such as 'tested safe to 1.5 teslas' or 'safe in magnetic fields below 500 gauss in strength').

MR Conditional sign

MR-Unsafe — Nearly self-explanatory, this category is reserved for objects that are significantly ferromagnetic and pose a clear and direct threat to persons and equipment within the magnet room.

The very high strength of the magnetic field can also cause "missile-effect" accidents, where ferromagnetic objects are attracted to the center of the magnet, and there have been incidences of injury and death.[37] [38] To reduce the risks of projectile accidents, ferromagnetic objects and devices are typically prohibited in proximity to the MRI scanner and patients undergoing MRI examinations are required to remove all metallic objects, often by changing into a gown or scrubs and ferromagnetic detection devices are used by some sites[39] [40]

There is no evidence for biological harm from even very powerful static magnetic fields[41]

MR Unsafe sign

Radio frequency energy

A powerful radio transmitter is needed for excitation of proton spins. This can heat the body to the point of risk of hyperthermia in patients, particularly in obese patients or those with thermoregulation disorders. Several countries have issued restrictions on the maximum specific absorption rate that a scanner may produce.

Peripheral nerve stimulation (PNS)

The rapid switching on and off of the magnetic field gradients is capable of causing nerve stimulation. Volunteers report a twitching sensation when exposed to rapidly switched fields, particularly in their extremities. The reason the peripheral nerves are stimulated is that the changing field increases with distance from the center of the gradient coils (which more or less coincides with the center of the magnet). Note however that when imaging the head, the heart is far off-center and induction of even a tiny current into the heart must be avoided at all costs. Although PNS was not a problem for the slow, weak gradients used in the early days of MRI, the strong, rapidly switched gradients used in techniques such as EPI, fMRI, diffusion MRI, etc. are indeed capable of inducing PNS. American and European regulatory agencies insist that manufacturers stay below specified $d\mathbf{B}/dt$ limits ($d\mathbf{B}/dt$ is the change in field per unit time) or else prove that no PNS is induced for any imaging sequence. As a result of $d\mathbf{B}/dt$ limitation, commercial MRI systems cannot use the full rated power of their gradient amplifiers.

Acoustic noise

Switching of field gradients causes a change in the Lorentz force experienced by the gradient coils, producing minute expansions and contractions of the coil itself. As the switching is typically in the audible frequency range, the resulting vibration produces loud noises (clicking or beeping). This is most marked with high-field machines[42] and rapid-imaging techniques in which sound intensity can reach 120 dB(A) (equivalent to a jet engine at take-off),[43] and therefore appropriate ear protection is essential for anyone inside the MRI scanner room during the examination.[44]

Cryogens

As described above in #Scanner construction and operation, many MRI scanners rely on cryogenic liquids to enable superconducting capabilities of the electromagnetic coils within. Though the cryogenic liquids used are non-toxic, their physical properties present specific hazards.

An unintentional shut-down of a superconducting electromagnet, an event known as "quench", involves the rapid boiling of liquid helium from the device. If the rapidly expanding helium cannot be dissipated through an external vent, sometimes referred to as 'quench pipe', it may be released into the scanner room where it may cause displacement of the oxygen and present a risk of asphyxiation.[45]

Liquid helium, the most commonly used cryogen in MRI, undergoes near explosive expansion as it changes from liquid to a gaseous state. Rooms built in support of superconducting MRI equipment should be equipped with pressure relief mechanisms[46] and an exhaust fan, in addition to the required quench pipe.

Since a quench results in rapid loss of all cryogens in the magnet, recommissioning the magnet is expensive and time-consuming. Spontaneous quenches are uncommon, but may also be triggered by equipment malfunction, improper cryogen fill technique, contaminants inside the cryostat, or extreme magnetic or vibrational disturbances.

Contrast agents

The most commonly used intravenous contrast agents are based on chelates of gadolinium. In general, these agents have proved safer than the iodinated contrast agents used in X-ray radiography or CT. Anaphylactoid reactions are rare, occurring in approx. 0.03–0.1%.[47] Of particular interest is the lower incidence of nephrotoxicity, compared with iodinated agents, when given at usual doses—this has made contrast-enhanced MRI scanning an option for patients with renal impairment, who would otherwise not be able to undergo contrast-enhanced CT.[48]

Although gadolinium agents have proved useful for patients with renal impairment, in patients with severe renal failure requiring dialysis there is a risk of a rare but serious illness, nephrogenic systemic fibrosis, that may be linked to the use of certain gadolinium-containing agents. The most frequently linked is gadodiamide, but other agents have been linked too.[49] Although a causal link has not been definitively established, current guidelines in the United States are that dialysis patients should only receive gadolinium agents where essential, and that dialysis should be performed as soon as possible after the scan to remove the agent from the body promptly.[50] In Europe, where more gadolinium-containing agents are available, a classification of agents according to potential risks has been released.[51] [52] Recently a new contrast agent named gadoxetate, brand name Eovist (US) or Primovist (EU), was approved for diagnostic use: this has the theoretical benefit of a dual excretion path.[53]

Pregnancy

No effects of MRI on the fetus have been demonstrated.[54] In particular, MRI avoids the use of ionizing radiation, to which the fetus is particularly sensitive. However, as a precaution, current guidelines recommend that pregnant women undergo MRI only when essential. This is particularly the case during the first trimester of pregnancy, as organogenesis takes place during this period. The concerns in pregnancy are the same as for MRI in general, but the fetus may be more sensitive to the effects—particularly to heating and to noise. However, one additional concern is the use of contrast agents; gadolinium compounds are known to cross the placenta and enter the fetal bloodstream, and it is recommended that their use be avoided.

Despite these concerns, MRI is rapidly growing in importance as a way of diagnosing and monitoring congenital defects of the fetus because it can provide more diagnostic information than ultrasound and it lacks the ionizing radiation of CT. MRI without contrast agents is the imaging mode of choice for pre-surgical, in-utero diagnosis and evaluation of fetal tumors, primarily teratomas, facilitating open fetal surgery, other fetal interventions, and planning for procedures (such as the EXIT procedure) to safely deliver and treat babies whose defects would otherwise be fatal.

Claustrophobia and discomfort

Due to the construction of some MRI scanners, they can be potentially unpleasant to lie in. Older models of closed bore MRI systems feature a fairly long tube or tunnel. The part of the body being imaged must lie at the center of the magnet, which is at the absolute center of the tunnel. Because scan times on these older scanners may be long (occasionally up to 40 minutes for the entire procedure), people with even mild claustrophobia are sometimes unable to tolerate an MRI scan without management. Modern scanners may have larger bores (up to 70 cm) and scan times are shorter. This means that claustrophobia is less of an issue, and many patients now find MRI an innocuous and easily tolerated procedure.

Nervous patients may still find the following strategies helpful:

- Advance preparation
  - visiting the scanner to see the room and practice lying on the table
  - visualization techniques
  - chemical sedation
  - general anesthesia

- Coping while inside the scanner
  - holding a "panic button"
  - closing eyes as well as covering them (e.g. washcloth, eye mask)
  - listening to music on headphones or watching a movie with a Head-mounted display while in the machine

Alternative scanner designs, such as open or upright systems, can also be helpful where these are available. Though open scanners have increased in popularity, they produce inferior scan quality because they operate at lower magnetic fields than closed scanners. However, commercial 1.5 tesla open systems have recently become available, providing much better image quality than previous lower field strength open models.[55]

For babies and young children chemical sedation or general anesthesia are the norm, as these subjects cannot be instructed to hold still during the scanning session. Obese patients and pregnant women may find the MRI machine to be a tight fit. Pregnant women may also have difficulty lying on their backs for an hour or more without moving.

Guidance

Safety issues, including the potential for biostimulation device interference, movement of ferromagnetic bodies, and incidental localized heating, have been addressed in the American College of Radiology's *White Paper on MR Safety,* which was originally published in 2002 and expanded in 2004. The *ACR White Paper on MR Safety* has been rewritten and was released early in 2007 under the new title *ACR Guidance Document for Safe MR Practices* [56].
In December 2007, the Medicines in Healthcare product Regulation Agency (MHRA), a UK healthcare regulatory body, issued their *Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use* [57].
In February 2008, the Joint Commission, a US healthcare accrediting organization, issued a Sentinel Event Alert #38 [58], their highest patient safety advisory, on MRI safety issues.
In July 2008, the United States Veterans Administration, a federal governmental agency serving the healthcare needs of former military personnel, issued a substantial revision to their *MRI Design Guide* [59], which includes physical or facility safety considerations.

The European Physical Agents Directive

The European Physical Agents (Electromagnetic Fields) Directive is legislation adopted in European legislature. Originally scheduled to be required by the end of 2008, each individual state within the European Union must include this directive in its own law by the end of 2012. Some member nations passed complying legislation and are now attempting to repeal their state laws in expectation that the final version of the EU Physical Agents Directive will be substantially revised prior to the revised adoption date.

The directive applies to occupational exposure to electromagnetic fields (not medical exposure) and was intended to limit workers' acute exposure to strong electromagnetic fields, as may be found near electricity substations, radio or television transmitters or industrial equipment. However, the regulations impact significantly on MRI, with separate sections of the regulations limiting exposure to static magnetic fields, changing magnetic fields and radio frequency energy. Field strength limits are given, which may not be exceeded. An employer may commit a criminal offense by allowing a worker to exceed an exposure limit, if that is how the Directive is implemented in a particular member state.

The Directive is based on the international consensus of established effects of exposure to electromagnetic fields, and in particular the advice of the European Commissions's advisor, the International Commission on Non-Ionizing Radiation Protection (ICNIRP). The aims of the Directive, and the ICNIRP guidelines it is based on, are to prevent exposure to potentially harmful fields. The actual limits in the Directive are very similar to the limits advised by the Institute of Electrical and Electronics Engineers, with the exception of the frequencies produced by the gradient coils, where the IEEE limits are significantly higher.

Many Member States of the EU already have either specific EMF regulations or (as in the UK) a general requirement under workplace health and safety legislation to protect workers against electromagnetic fields. In almost all cases

the existing regulations are aligned with the ICNIRP limits so that the Directive should, in theory, have little impact on any employer already meeting their legal responsibilities.

The introduction of the Directive has brought to light an existing potential issue with occupational exposures to MRI fields. There are at present very few data on the number or types of MRI practice that might lead to exposures in excess of the levels of the Directive.[60] [61] There is a justifiable concern amongst MRI practitioners that if the Directive were to be enforced more vigorously than existing legislation, the use of MRI might be restricted, or working practices of MRI personnel might have to change.

In the initial draft a limit of static field strength to 2 T was given. This has since been removed from the regulations, and whilst it is unlikely to be restored as it was without a strong justification, some restriction on static fields may be reintroduced after the matter has been considered more fully by ICNIRP. The effect of such a limit might be to restrict the installation, operation and maintenance of MRI scanners with magnets of 2 T and stronger. As the increase in field strength has been instrumental in developing higher resolution and higher performance scanners, this would be a significant step back. This is why it is unlikely to happen without strong justification.

Individual government agencies and the European Commission have now formed a working group to examine the implications on MRI and to try to address the issue of occupational exposures to electromagnetic fields from MRI.

Three-dimensional (3D) image reconstruction

The principle

Because contemporary MRI scanners offer isotropic, or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by 'stacking' the individual slices one on top of the other. The program may then display the volume in an alternative manner.

3D rendering techniques

Surface rendering

> A threshold value of greyscale density is chosen by the operator (e.g. a level that corresponds to fat). A threshold level is set, using edge detection image processing algorithms. From this, a 3-dimensional model can be constructed and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

> Surface rendering is limited in that it only displays surfaces that meet a threshold density, and only displays the surface closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image - e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

Image segmentation

Where different structures have similar threshold density, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

2003 Nobel Prize

Reflecting the fundamental importance and applicability of MRI in medicine, Paul Lauterbur of the University of Illinois at Urbana-Champaign and Sir Peter Mansfield of the University of Nottingham were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging". The Nobel citation acknowledged Lauterbur's insight of using magnetic field gradients to determine spatial localization, a discovery that allowed rapid acquisition of 2D images. Mansfield was credited with introducing the mathematical formalism and developing techniques for efficient gradient utilization and fast imaging. The actual research that won the prize was done almost 30 years before, while Paul Lauterbur was at Stony Brook University in New York.

The award was vigorously protested by Raymond Vahan Damadian, founder of FONAR Corporation, who claimed that he invented the MRI,[3] and that Lauterbur and Mansfield had merely refined the technology.[62] An ad hoc group, called "The Friends of Raymond Damadian", took out full-page advertisements in the *New York Times* and *The Washington Post* entitled "The Shameful Wrong That Must Be Righted", demanding that he be awarded at least a share of the Nobel Prize.[63] Also, even earlier, in the Soviet Union, Vladislav Ivanov filed (in 1960) a document with the USSR State Committee for Inventions and Discovery at Leningrad for a Magnetic Resonance Imaging device,[64] although this was not approved until the 1970s.[65] In a letter to *Physics Today*, Herman Carr pointed out his own even earlier use of field gradients for one-dimensional MR imaging.[66]

See also

- Earth's field NMR (EFNMR)
- Electron-spin resonance (spin physics)
- History of brain imaging
- Medical imaging
- Magnetic immunoassay
- Jemris (open source MRI simulator)
- *Magnetic Resonance Imaging (journal)*
- Magnetic resonance microscopy
- Magnetic Particle Imaging (MPI)
- Magnetic resonance elastography
- Neuroimaging software
- Nephrogenic fibrosing dermopathy
- Nobel Prize controversies
- Nuclear magnetic resonance (NMR)
- 2D-FT NMRI and Spectroscopy
- Relaxation
- Robinson oscillator
- Rabi cycle
- Virtopsy

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External links

- A Guided Tour of MRI: An introduction for laypeople (http://www.magnet.fsu.edu/education/tutorials/magnetacademy/mri/) National High Magnetic Field Laboratory
- The Basics of MRI (http://www.cis.rit.edu/htbooks/mri/). *Underlying physics and technical aspects*.
- Video: What to Expect During Your MRI Exam (http://www.imrser.org/PatientVideo.html) from the Institute for Magnetic Resonance Safety, Education, and Research (IMRSER)
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- Trends in Biotechnology Volume 28, Issue 7, July 2010, Pages 363-370 (http://dx.doi.org/10.1016/j.tibtech.2010.04.002)
- Blue Plaque commemorating the manufacture of the first commercial MRI whole body scanner at Osney Mead, Oxford (http://www.oxfordshireblueplaques.org.uk/plaques/mri.html)
- Royal Institution Lecture - MRI: A Window on the Human Body (http://www.vega.org.uk/video/programme/73)

Advanced Experimental Techniques and Methods

Optical Tomography and Imaging

Optical imaging is an imaging technique.

Optics usually describes the behavior of visible, ultraviolet, and infrared light used in imaging.

Because light is an electromagnetic wave, similar phenomena occur in X-rays, microwaves, radio waves. Chemical imaging or molecular imaging [1] [2] [3] involves inference from the deflection of light emitted from (e.g. laser, infrared) source to structure, texture, anatomic and chemical properties of material (e.g. crystal, cell tissue). Optical imaging systems may be divided into diffusive [4] and ballistic imaging [5] systems.

Diffusive optical imaging in neuroscience

Diffusive optical imaging (also known as *Near Infrared Optical Tomography* or NIROT) is a technique that gives neuroscientists the ability to simultaneously obtain information about the source of neural activity as well as its time course. In other words, it allows them to "see" neural activity and study the functioning of the brain.

In this method, a near-infrared laser is positioned on the scalp. Detectors composed of optical fiber bundles are located a few centimeters away from the light source. These detectors sense how the path of light is altered, either through absorption or scattering, as it traverses brain tissue.

This method can provide two types of information. First, it can be used to measure the absorption of light, which is related to concentration of chemicals in the brain. Second, it can measure the scattering of light, which is related to physiological characteristics such as the swelling of glia and neurons that are associated with neuronal firing.

Typical applications include rapid 2D optical *topographic* imaging of the event-related optical signal (EROS) or Near infrared spectroscopy (NIRS) signal following brain activity and *tomographic* reconstruction of an entire 3D volume of tissue to diagnose breast cancer or neonatal brain haemorrhage. The spatial resolution of DOT techniques is several millimeters, comparable to the lower end of functional magnetic resonance imaging (fMRI). The temporal resolution of EROS is very good, comparable to electroencephalography, and magnetoencephalography (~milliseconds), while that of NIRS, which measures hemodynamic changes rather than neuronal activity, is comparable to fMRI (~seconds). DOT instruments are relatively low cost ($150,000), portable and immune to electrical interference. The signal-to-noise ratio of NIRS is quite good, enabling detection of responses to single events in many cases. EROS signals are much weaker, typically requiring averaging of many responses.

Important chemicals that this method can detect include hemoglobin and cytochromes.

Ballistic optical imaging

Ballistic optical imaging systems ignore the diffused photons and rely only on the ballistic photons to create high-resolution (near diffraction limited) images through scattering media.

See also

- Photon diffusion
- Ballistic imaging
- Photon diffusion equation

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External links

- Understanding Near-Infrared Imaging (http://www.licor.com/bio/products/imaging_systems/pearl/pearl_sensitivity.jsp/) – Resource to better understand the benefits of Near-Infrared imaging.
- Diffuse Optics Lab at University of Pennsylvania, Philadelphia (http://www.lrsm.upenn.edu/pmi)
- DOI at Massachusetts General Hospital, Boston (http://www.nmr.mgh.harvard.edu/martinos/research/technologiesDOI.php)
- Biomedical Imaging Group at Dartmouth (http://www-nml.dartmouth.edu/biomedprg/biomed.html)
- DOS/I Lab at the Beckman Laser Institute, University of California, Irvine (http://dosi.bli.uci.edu)
- A review article in the field by A.P. Gibson et al. (http://www.iop.org/EJ/abstract/0031-9155/50/4/R01)
- An article on optical breast imaging (http://medicalphysicsweb.org/cws/article/research/27299)
- Illinois ECE 460 Principles of Optical Imaging (http://nanohub.org/resources/5163) Course lecture notes

Fourier transform spectroscopy

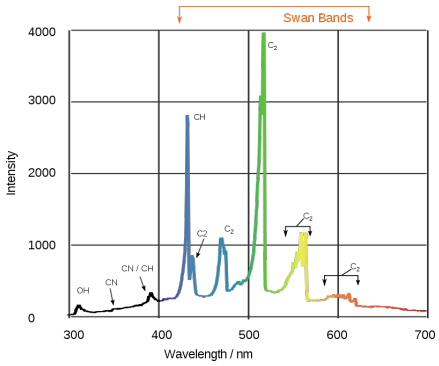
Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the coherence of a radiative source, using time-domain or space-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FTIR, FT-NIRS), nuclear magnetic resonance (NMR) and magnetic resonance spectroscopic imaging (MRSI)[1] , mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light (see: field-autocorrelation), including the continuous wave *Michelson* or *Fourier transform* spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

The term *Fourier transform spectroscopy* reflects the fact that in all these techniques, a Fourier transform is required to turn the raw data into the actual spectrum, and in many of the cases in optics involving interferometers, is based on the Wiener–Khinchin theorem.

Conceptual introduction

Measuring an emission spectrum

One of the most basic tasks in spectroscopy is to characterize the spectrum of a light source: How much light is emitted at each different wavelength. The most straightforward way to measure a spectrum is to pass the light through a monochromator, an instrument that blocks all of the light *except* the light at a certain wavelength (the un-blocked wavelength is set by a knob on the monochromator). Then the intensity of this remaining (single-wavelength) light is measured. The measured intensity directly indicates how much light is emitted at that wavelength. By varying the monochromator's wavelength setting, the full spectrum can be measured. This simple scheme in fact describes how *some* spectrometers work.



An example of a spectrum: The spectrum of light emitted by the blue flame of a butane torch. The horizontal axis is the wavelength of light, and the vertical axis represents how much light is emitted by the torch at that wavelength.

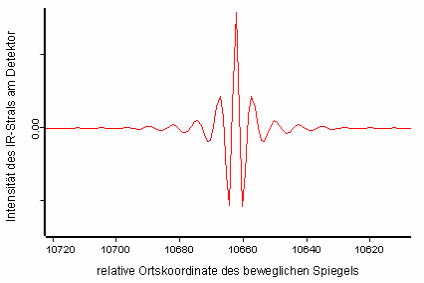
Fourier transform spectroscopy is a less intuitive way to get the same information. Rather than allowing only one wavelength at a time to pass through to the detector, this technique lets through a beam containing many different wavelengths of light at once, and measures the *total* beam intensity. Next, the beam is modified to contain a *different* combination of wavelengths, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer how much light there is at each wavelength.

To be more specific, between the light source and the detector, there is a certain configuration of mirrors that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that can pass through.

As mentioned, computer processing is required to turn the raw data (light intensity for each mirror position) into the desired result (light intensity for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".

Measuring an absorption spectrum

The method of Fourier transform spectroscopy can also be used for absorption spectroscopy. The primary example is "FTIR Spectroscopy", a common technique in chemistry.



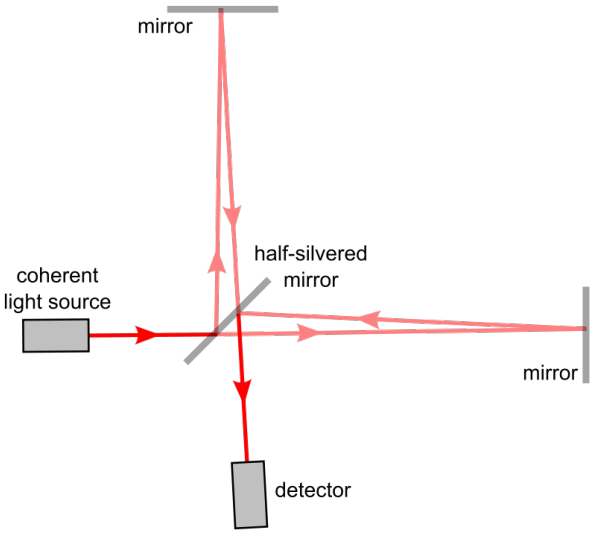
An "interferogram" from a Fourier transform spectrometer. The horizontal axis is the position of the mirror, and the vertical axis is the amount of light detected. This is the "raw data" which can be Fourier transformed into an actual spectrum.

In general, the goal of absorption spectroscopy is to measure how well a sample absorbs or transmits light at each different wavelength. Although absorption spectroscopy and emission spectroscopy are different in principle, they are closely related in practice; any technique for emission spectroscopy can also be used for absorption spectroscopy. First, the emission spectrum of a broadband lamp is measured (this is called the "background spectrum"). Second, the emission spectrum of the same lamp *shining through the sample* is measured (this is called the "sample spectrum"). The sample will absorb some of the light, causing the spectra to be different. The ratio of the "sample spectrum" to the "background spectrum" is directly related to the sample's absorption spectrum.

Accordingly, the technique of "Fourier transform spectroscopy" can be used both for measuring emission spectra (for example, the emission spectrum of a star), *and* absorption spectra (for example, the absorption spectrum of a glass of liquid).

Continuous wave *Michelson* or *Fourier transform* spectrograph

The Michelson spectrograph is similar to the instrument used in the Michelson-Morley experiment. Light from the source is split into two beams by a half-silvered mirror, one is reflected off a fixed mirror and one off a moving mirror which introduces a time delay—the Fourier transform spectrometer is just a Michelson interferometer with a movable mirror. The beams interfere, allowing the temporal coherence of the light to be measured at each different time delay setting, effectively converting the time domain into a spatial coordinate. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light. Michelson spectrographs are capable of very high spectral resolution observations of very bright sources. The Michelson or Fourier transform spectrograph was popular for infra-red applications at a time when infra-red astronomy only had single pixel detectors. Imaging Michelson spectrometers are a possibility, but in general have been supplanted by imaging Fabry–Pérot instruments which are easier to construct.



The Fourier transform spectrometer is just a Michelson interferometer but one of the two fully-reflecting mirrors is movable, allowing a variable delay (in the travel-time of the light) to be included in one of the beams.

Extracting the spectrum

The intensity as a function of the path length difference in the interferometer p and wavenumber $\tilde{\nu} = 1/\lambda$ is [2]

$$I(p, \tilde{\nu}) = I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)],$$

where $I(\tilde{\nu})$ is the spectrum to be determined. Note that it is not necessary for $I(\tilde{\nu})$ to be modulated by the sample before the interferometer. In fact, most FTIR spectrometers place the sample after the interferometer in the optical path. The total intensity at the detector is

$$I(p) = \int_0^\infty I(p, \tilde{\nu}) d\tilde{\nu} = \int_0^\infty I(\tilde{\nu})[1 + \cos(2\pi\tilde{\nu}p)] d\tilde{\nu}.$$

This is just a Fourier cosine transform. The inverse gives us our desired result in terms of the measured quantity $I(p)$:

$$I(\tilde{\nu}) = 4 \int_0^\infty [I(p) - \tfrac{1}{2} I(p = 0)] \cos(2\pi\tilde{\nu}p) dp.$$

Pulsed *Fourier transform* spectrometer

A pulsed *Fourier transform* spectrometer does not employ transmittance techniques. In the most general description of pulsed FT spectrometry, a sample is exposed to an energizing event which causes a periodic response. The frequency of the periodic response, as governed by the field conditions in the spectrometer, is indicative of the measured properties of the analyte.

Examples of pulsed Fourier transform spectrometry

In magnetic spectroscopy (EPR, NMR), an RF pulse in a strong ambient magnetic field is used as the energizing event. This turns the magnetic particles at an angle to the ambient field, resulting in gyration. The gyrating spins then induce a periodic current in a detector coil. Each spin exhibits a characteristic frequency of gyration (relative to the field strength) which reveals information about the analyte.

In Fourier transform mass spectrometry, the energizing event is the injection of the charged sample into the strong electromagnetic field of a cyclotron. These particles travel in circles, inducing a current in a fixed coil on one point in their circle. Each traveling particle exhibits a characteristic cyclotron frequency-field ratio revealing the masses in the sample.

Free induction decay

Pulsed FT spectrometry gives the advantage of requiring a single, time-dependent measurement which can easily deconvolute a set of similar but distinct signals. The resulting composite signal, is called a *free induction decay,* because typically the signal will decay due to inhomogeneities in sample frequency, or simply unrecoverable loss of signal due to entropic loss of the property being measured.

Stationary forms of Fourier transform spectrometers

In addition to the scanning forms of Fourier transform spectrometers, there are a number of stationary or self-scanned forms.[3] While the analysis of the interferometric output is similar to that of the typical scanning interferometer, significant differences apply,as shown in the published analyses. Some stationary forms retain the Fellgett multiplex advantage, and their use in the spectral region where detector noise limits apply is similar to the scanning forms of the FTS. In the photon-noise limited region, the application of stationary interferometers is dictated by specific consideration for the spectral region and the application.

Fellgett advantage

One of the most important advantages of Fourier transform spectroscopy was shown by P.B. Fellgett, an early advocate of the method. The Fellgett advantage, also known as the multiplex principle, states that when obtaining a spectrum when measurement noise is dominated by detector noise, a multiplex spectrometer such as a Fourier transform spectrometer will produce a relative improvement in signal-to-noise ratio, compared to an equivalent scanning monochromator, of the order of the square root of m, where m is the number of sample points comprising the spectrum.

Converting spectra from time domain to frequency domain

$$S(t) = \int_{-\infty}^{\infty} I(\nu) e^{-i\nu 2\pi t}\, d\nu$$

The sum is performed over all contributing frequencies to give a signal S(t) in the time domain.

$$I(\nu) = \int_{-\infty}^{\infty} S(t) e^{i\nu 2\pi t} dt$$

gives non-zero value when S(t) contains a component that matches the oscillating function.
Remember that

$$e^{ix} = \cos x + i \sin x$$

See also

- Applied spectroscopy
- Forensic chemistry
- Forensic polymer engineering
- Nuclear Magnetic Resonance
- Infrared spectroscopy

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[2] Peter Atkins, Julio De Paula. 2006. *Physical Chemistry*, 8th ed. Oxford University Press: Oxford, UK.
[3] William H. Smith U.S. Patent 4976542 (http://www.google.com/patents?vid=4976542) Digital Array Scanned Interferometer, issued Dec. 11, 1990

External links

- Description of how a Fourier transform spectrometer works (http://scienceworld.wolfram.com/physics/FourierTransformSpectrometer.html)
- The Michelson or Fourier transform spectrograph (http://www.astro.livjm.ac.uk/courses/phys362/notes/)
- Internet Journal of Vibrational Spectroscopy - How FTIR works (http://www.ijvs.com/volume5/edition5/section1.html#Feature)
- Fourier Transform Spectroscopy Topical Meeting and Tabletop Exhibit (http://www.osa.org/meetings/topicalmeetings/fts/default.aspx)

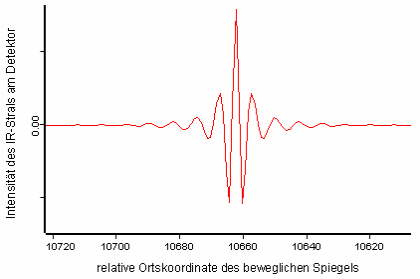
FT-Near Infrared Spectroscopy and Imaging

Fourier transform infrared spectroscopy (**FTIR**)[1] is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. An FTIR spectrometer simultaneously collects spectral data in a wide spectral range. This confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time. FTIR technique has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared) and opened up new applications of infrared spectroscopy.

The term *Fourier transform infrared spectroscopy* originates from the fact that a Fourier transform (a mathematical algorithm) is required to convert the raw data into the actual spectrum. For other uses of this kind of technique, see Fourier transform spectroscopy.

Conceptual introduction

The goal of any absorption spectroscopy (FTIR, ultraviolet-visible ("UV-Vis") spectroscopy, etc.) is to measure how well a sample absorbs light at each wavelength. The most straightforward way to do this, the "dispersive spectroscopy" technique, is to shine a monochromatic light beam at a sample, measure how much of the light is absorbed, and repeat for each different wavelength. (This is how UV-Vis spectrometers work, for example.)



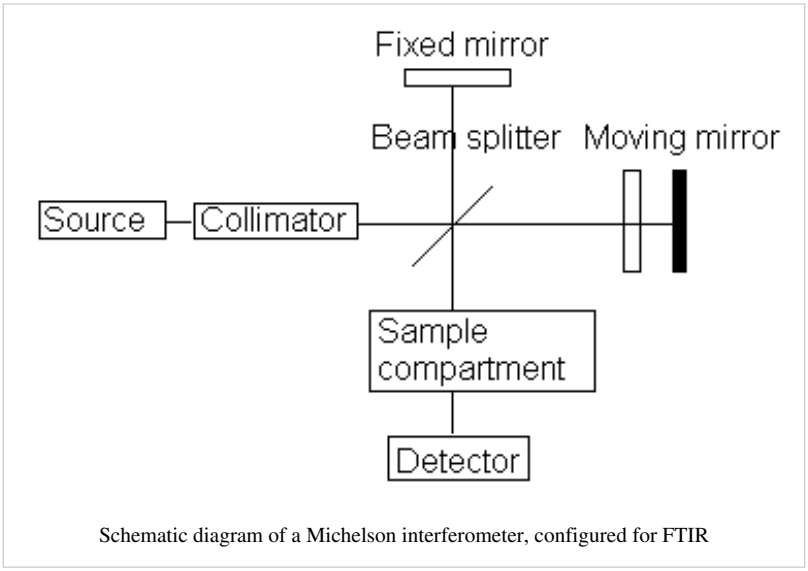
An interferogram from an FTIR spectrometer. The horizontal axis is the position of the mirror, and the vertical axis is the amount of light detected. This is the "raw data" which can be transformed into an actual spectrum.

Fourier transform spectroscopy is a less intuitive way to obtain the same information. Rather than shining a *monochromatic* beam of light at the sample, this technique shines a beam containing many different frequencies of light at once, and measures how much of that beam is absorbed by the sample. Next, the beam is modified to contain a different combination of frequencies, giving a second data point. This process is repeated many times. Afterwards, a computer takes all this data and works backwards to infer what the absorption is at each wavelength.

The beam described above is generated by starting with a broadband light source—one containing the full spectrum of wavelengths to be measured. The light shines into a certain configuration of mirrors, called a Michelson interferometer, that allows some wavelengths to pass through but blocks others (due to wave interference). The beam is modified for each new data point by moving one of the mirrors; this changes the set of wavelengths that pass through.

As mentioned, computer processing is required to turn the raw data (light absorption for each mirror position) into the desired result (light absorption for each wavelength). The processing required turns out to be a common algorithm called the Fourier transform (hence the name, "Fourier transform spectroscopy"). The raw data is sometimes called an "interferogram".

Michelson interferometer



Schematic diagram of a Michelson interferometer, configured for FTIR

In a Michelson interferometer adapted for FTIR, light from the polychromatic infrared source, approximately a black-body radiator, is collimated and directed to a beam splitter. Ideally 50% of the light is reflected towards the fixed mirror and 50% is transmitted towards the moving mirror. Light is reflected from the two mirrors back to the beam splitter and (ideally) 50% of the original light passes into the sample compartment. There, the light is focussed on the sample. On leaving the sample compartment the light is refocused on to the detector. The difference in optical path length between the two arms to the interferometer is known as the retardation. An interferogram is obtained by varying the retardation and recording the signal from the detector for various values of the retardation. The form of the interferogram when no sample is present depends on factors such as the variation of source intensity and splitter efficiency with wavelength. This results in a maximum at zero retardation, when there is constructive interference at all wavelengths, followed by series of "wiggles". The position of zero retardation is determined accurately by finding the point of maximum intensity in the interferogram. When a sample is present the background interferogram is modulated by the presence of absorption bands in the sample.

There are two principle advantages for a FT spectrometer compared to a scanning (dispersive) spectrometer.[2] [3]

1. The multiplex or Fellgett's advantage. This arises from the fact that information from all wavelengths is collected simultaneously. It results in a higher Signal-to-noise ratio for a given scan-time or a shorter scan-time for a given resolution.
2. The throughput or Jacquinot's advantage. This results from the fact that, in a dispersive instrument, the monochromator has entrance and exit slits which restrict the amount of light that passes through it. The interferometer throughput is determined only by the diameter of the collimated beam coming from the source.

Other minor advantages include less sensitivity to stray light,[3] and "Connes' advantage" (better wavelength accuracy)[3] , while a disadvantage is that FTIR cannot use the advanced electronic filtering techniques that often makes its signal-to-noise ratio inferior to that of dispersive measurements.[3]

Resolution

The interferogram belongs in the length domain. Fourier transform (FT) inverts the dimension, so the FT of the interferogram belongs in the reciprocal length domain, that is the wavenumber domain. The spectral resolution in wavenumbers per cm is equal to the reciprocal of the maximum retardation in cm. Thus a 4 cm^{-1} resolution will be obtained if the maximum retardation is 0.25 cm; this is typical of the cheaper FTIR instruments. Much higher resolution can be obtained by increasing the maximum retardation. This is not easy as the moving mirror must travel in a near-perfect straight line. The use of corner-cube mirrors in place of the flat mirrors is helpful as an outgoing ray from a corner-cube mirror is parallel to the incoming ray, regardless of the orientation of the mirror about axes perpendicular to the axis of the light beam. Connes measured in 1966 the temperature of the atmosphere of Venus by recording the vibration-rotation spectrum of Venusian CO_2 at 0.1 cm^{-1} resolution.[4] Michelson himself attempted to resolve the hydrogen H_α emission band in the spectrum of a hydrogen atom into its two components by using his

interferometer.[1] p25 A spectrometer with 0.001 cm^{-1} resolution is now available commercially from Bruker. The throughput advantage is important for high-resolution FTIR as the monochromator in a dispersive instrument with the same resolution would have very narrow entrance and exit slits.

Beam splitter

The beam-splitter can not be made of a common glass, as it is opaque to infrared radiation of wavelengths longer than about 2.5 μm. A thin film, usually of a plastic material, is used instead. However, as any material has a limited range of optical transmittance, several beam-splitters are used interchangeably to cover a wide spectral range.

Fourier transform

The interferogram in practice consists of a set of intensities measured for discrete values of retardation. The difference between successive retardation values is constant. Thus, a discrete Fourier transform is needed. The fast Fourier transform (FFT) algorithm is used.

Far-infrared FTIR

The first FTIR spectrometers were developed for far-infrared range. The reason for this has to do with the mechanical tolerance needed for good optical performance, which is related to the wavelength of the light being used. For the relatively long wavelengths of the far infrared (~10 μm), tolerances are adequate, whereas for the rock-salt region tolerances have to be better than 1 μm. A typical instrument was the cube interferometer developed at the NPL[5] and marketed by Grubb Parsons. It used a stepper motor to drive the moving mirror, recording the detector response after each step was completed.

Mid-infrared FTIR

With the advent of cheap microcomputers it became possible to have a computer dedicated to controlling the spectrometer, collecting the data, doing the Fourier transform and presenting the spectrum. This provided the impetus for the development of FTIR spectrometers for the rock-salt region. The problems of manufacturing ultra-high precision optical and mechanical components had to be solved. A wide range of instrument is now available commercially. Although instrument design has become more sophisticated, the basic principles remain the same. Nowadays, the moving mirror of the interferrometer moves at a constant velocity, and sampling of the interferogram is triggered by finding zero-crossings in the fringes of a secondary interferometer lit by a helium-neon laser. This confers high wavenumber accuracy on the resulting infrared spectrum and avoids wavenumber calibration errors.

Near-infrared FTIR

The near-infrared region spans the wavelength range between the rock-salt region and the start of the visible region at about 750 nm. Overtones of fundamental vibrations can be observed in this region. It is used mainly in industrial applications such as process control.

Applications

FTIR can be used in all applications where a dispersive spectrometer was used in the past (see external links). In addition, the multiplex and throughput advantages have opened up new areas of application. These include:

- GC-IR (gas chromatography-infrared spectrometry). A gas chromatograph can be used to separate the components of a mixture. The fractions containing single components are directed into an FTIR spectrometer, to provide the infrared spectrum of the sample. This technique is complementary to GC-MS (gas

chromatography-mass spectrometry). The GC-IR method is particularly useful for identifying isomers, which by their nature have identical masses. The key to the successful use of GC-IR is that the interferogram can be captured in a very short time, typically less than 1 second. FTIR has also been applied to the analysis of liquid chromatography fractions.[3]

- TG-IR (thermogravimetry-infrared spectrometry) IR spectra of the gases evolved during thermal decompostion are obtained as a function of temperature.[6]
- Micro-samples. Tiny samples, such as in forensic analysis, can be examined with the aid of an infrared microscope in the sample chamber. An image of the surface can be obtained by scanning.[7] Another example is the use of FTIR to characterize artistic materials in old-master paintings.[8]
- Emission spectra. Instead of recording the spectrum of light transmitted through the sample, FTIR spectrometer can be used to acquire spectrum of light emitted by the sample. Such emission could be induced by various processes, and the most common ones are luminescence and Raman scattering. Little modification is required to an absorption FTIR spectrometer to record emission spectra and therefore many commercial FTIR spectrometers combine both absorption and emission/Raman modes.[9]
- Photocurrent spectra. This mode uses a standard, absorption FTIR spectrometer. The studied sample is placed instead of the FTIR detector, and its photocurrent, induced by the spectrometer's broadband source, is used to record the interferrogram, which is then converted into the photoconductivity spectrum of the sample.[10]

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External links

- Infracord spectrometer (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC441765/pdf/jcinvest00449-0191.pdf) photograph
- The Grubb-Parsons-NPL cube interferometer Spectroscopy, part 2 by Dudley Williams, page 81 (http://books.google.co.uk/books?id=XTolQEkzSR0C&pg=PA93&lpg=PA93&dq=grubb+parsons+cube&source=bl&ots=l0Sm8klxHG&sig=SzKdjgTB8YPyitRgAAlwH2zIOlo&hl=en&ei=w6lRTM-BNYaD4QaC48ygAw&sa=X&oi=book_result&ct=result&resnum=9&ved=0CDgQ6AEwCA#v=onepage&q=grubb parsons cube&f=false)
- FTIR application notes (http://las.perkinelmer.com/Catalog/TechLibDetails.htm?expand=Application&20Notes&ObjectId=FTIR+&+FTNIR+Spectrometers&CategoryID=FTIR+&+FTNIR+Spectrometers&type=CATEGORY) from Perkin Elmer

- FTIR application notes (http://www.varianinc.com/cgi-bin/nav?applications/ftir&cid=LNHOMKLPFQ) from Varian
- Infrared / FTIR Application Notes (http://www.selectscience.net/infrared-+-ftir/application-notes) Recent publications.
- Semiconductor applications (http://www.piketech.com/technical/application-pdfs/SemiconductorApplOverview.pdf) FTIR Sampling Techniques Overview.
- infrared materials (http://infrared.als.lbl.gov/content/web-links/58-irwindows) Properties of many salt crystals and useful links.

Chemical imaging

Chemical imaging (as quantitative - *chemical mapping*) is the analytical capability to create a visual image of components distribution from simultaneous measurement of spectra and spatial, time informations. [1] [2]

The main idea - for chemical imaging, the analyst may choose to take as many data spectrum measured at a particular chemical component in spatial location at time; this is useful for chemical identification and quantification. Alternatively, selecting an image plane at a particular data spectrum (PCA - multivariable data of wavelength, spatial location at time) can mapp the spatial distribution of sample components, provided that their spectral signatures are different at the selected data spectrum.

Software for chemical imaging is most specific and distinguished from chemical methods as the chemometrics.

Imaging technique is most often applied to either solid or gel samples, and has applications in chemistry, biology[3] [4] [5] [6] [7] [8] , medicine[9] [10] , pharmacy[11] (see also for example: Chemical Imaging Without Dyeing [12]), food science, biotechnology[13] [14] , agriculture and industry (see for example:NIR Chemical Imaging in Pharmaceutical Industry [15] and Pharmaceutical Process Analytical Technology: [16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Many imaging techniques can be used to analyze samples of all sizes, from the single molecule[17] [18] to the cellular level in biology and medicine[19] [20] [21] , and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (lambda) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients – a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the 'what' and the 'where' must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques is critical to understanding modern manufactured products and in some casses is a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected – either before or after interacting with the sample. Wavelength selection can be accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collected tens of thousands of spectra simultaneously is orders of magnitude faster than linear arrays which are can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

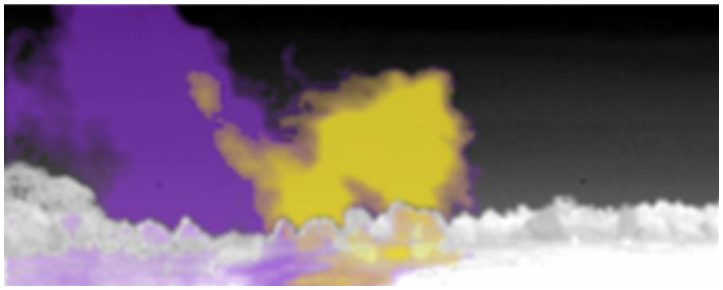
Types of vibrational chemical imaging instruments

Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500-25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, 4,000 – 400 cm^{-1}. The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see Microscopy#Infrared microscopy.



Remote chemical imaging of a simultaneous release of SF_6 and NH_3 at 1.5km using the FIRST imaging spectrometer[22]

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer distances. Target molecules can then be viewed using the selective absorption/emission processes described above. An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.

Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials[23] [24] . NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1}; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM obsevations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples[25] Furthermore, two-photon excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

See also

- Multispectral image
- Microspectroscopy
- Imaging spectroscopy

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14. FLIM Applications: (http://www.nikoninstruments.com/infocenter.php?n=FLIM) "FLIM is able to discriminate between fluorescence emanating from different fluorophores and autoflorescing molecules in a specimen, even if their emission spectra are similar. It is, therefore, ideal for identifying fluorophores in multi-label studies. FLIM can also be used to measure intracellular ion concentrations without extensive calibration procedures (for example, Calcium Green) and to obtain information about the local environment of a fluorophore based on changes in its lifetime." FLIM is also often used in microspectroscopic/chemical imaging, or microscopic, studies to monitor spatial and temporal protein-protein interactions, properties of membranes and interactions with nucleic acids in living cells.
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External links

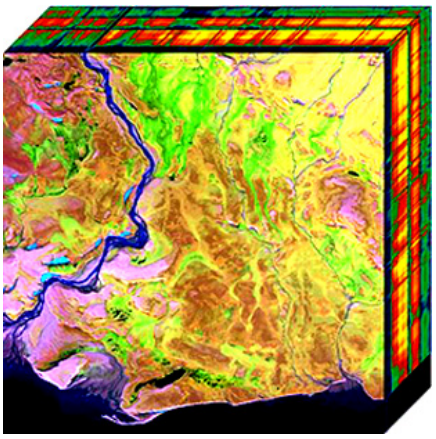
- NIR Chemical Imaging in Pharmaceutical Industry (http://www.spectroscopyeurope.com/NIR_14_3.pdf)
- Pharmaceutical Process Analytical Technology: (http://www.fda.gov/cder/OPS/PAT.htm)
- NIR Chemical Imaging for Counterfeit Pharmaceutical Product Analysis (http://www.spectroscopymag.com/spectroscopy/Near-IR+Spectroscopy/NIR-Chemical-Imaging-for-Counterfeit-Pharmaceutica/ArticleStandard/Article/detail/406629)
- Chemical Imaging: Potential New Crime Busting Tool (http://www.sciencedaily.com/releases/2007/08/070802103435.htm)
- Applications of Chemical Imaging in Research (http://www3.imperial.ac.uk/vibrationalspectroscopyandchemicalimaging/research)

Hyperspectral imaging

Hyperspectral imaging collects and processes information from across the electromagnetic spectrum. Unlike the human eye, which just sees visible light, hyperspectral imaging is more like the eyes of the mantis shrimp, which can see visible light as well as from the ultraviolet to infrared. Hyperspectral capabilities enable the mantis shrimp to recognize different types of coral, prey, or predators, all of which may appear as the same color to the human eye.

Humans build sensors and processing systems to provide the same type of capability for application in agriculture, mineralogy, physics, and surveillance. Hyperspectral sensors look at objects using a vast portion of the electromagnetic spectrum. Certain objects leave unique 'fingerprints' across the electromagnetic spectrum. These 'fingerprints' are known as spectral signatures and enable identification of the materials that make up a scanned object. For example, having the spectral signature for oil helps mineralogists find new oil fields.

Acquisition and Analysis



Example of a hyperspectral cube

Hyperspectral sensors collect information as a set of 'images'. Each image represents a range of the electromagnetic spectrum and is also known as a spectral band. These 'images' are then combined and form a three dimensional hyperspectral cube for processing and analysis.

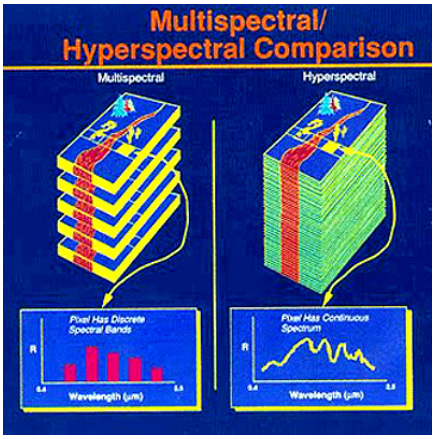
Hyperspectral cubes are generated from airborne sensors like the NASA's *Airborne Visible/Infrared Imaging Spectrometer* (AVIRIS), or from satellites like NASA's Hyperion.[1] However, for many development and validation studies handheld sensors are used.[2]

The precision of these sensors is typically measured in spectral resolution, which is the width of each band of the spectrum that is captured. If the scanner picks up on a large number of fairly narrow frequency bands, it is possible to identify objects even if said objects are only captured in a handful of pixels. However, spatial resolution is a factor in addition to spectral resolution. If the pixels are too large, then multiple objects are captured in the same pixel and become difficult to identify. If the pixels are too small, then the energy captured by each sensor-cell is low, and the decreased signal-to-noise ratio reduces the reliability of measured features.

MicroMSI, Opticks and Envi are three remote sensing applications that support the processing and analysis of hyperspectral data. The acquisition and processing of hyperspectral images is also referred to as imaging spectroscopy.

Differences between hyperspectral and multispectral imaging

Hyperspectral imaging is part of a class of techniques commonly referred to as spectral imaging or spectral analysis. Hyperspectral imaging is related to multispectral imaging. The distinction between hyper- and multi-spectral should not be based on a random or arbitrary "number of bands". A distinction that is based on the type of measurement may be more appropriate.



Hyperspectral and Multispectral Differences.

Multispectral deals with several images at discrete and somewhat narrow bands. The "discrete and somewhat narrow" is what distinguishes multispectral in the visible from color photography. A multispectral sensor may have many bands covering the spectrum from the visible to the longwave infrared. Multispectral images do not produce the "spectrum" of an object. Landsat is an excellent example.

Hyperspectral deals with imaging narrow spectral bands over a contiguous spectral range, and produce the spectra of all pixels in the scene. So a sensor with only 20 bands can also be hyperspectral when it covers the range from 500 to 700 nm with 20 10-nm wide bands. (While a sensor with 20 discrete bands covering the VIS, NIR, SWIR, MWIR, and LWIR would be considered multispectral.)

Ultraspectral could be reserved for interferometer type imaging sensors with a very fine spectral resolution. These sensor often have (but not necessarily) a low spatial resolution of several pixels only, a restriction imposed by the high data rate.

Applications

Hyperspectral remote sensing is used in a wide array of real-life applications. Although originally developed for mining and geology (the ability of hyperspectral imaging to identify various minerals makes it ideal for the mining and oil industries, where it can be used to look for ore and oil[2] [3]) it has now spread into fields as widespread as ecology and surveillance, as well as historical manuscript research such as the imaging of the Archimedes Palimpsest. This technology is continually becoming more available to the public, and has been used in a wide variety of ways. Organizations such as NASA and the USGS have catalogues of various minerals and their spectral signatures, and have posted them online to make them readily available for researchers.

Agriculture

Although the costs of acquiring hyperspectral images is typically high, for specific crops and in specific climates hyperspectral remote sensing is used more and more for monitoring the development and health of crops. In Australia work is under way to use imaging spectrometers to detect grape variety, and develop an early warning system for disease outbreaks.[4] Furthermore work is underway to use hyperspectral data to detect the chemical composition of plants[5] which can be used to detect the nutrient and water status of wheat in irrigated systems[6] .

Another important area in agriculture is the detection of animal proteins in compound feeds in order to avoid the Bovine spongiform encephalopathy (BSE) or mad-cow disease (MCD). For this, different studies have been done in order to propose alternative tools to the reference method (classical microscopy). One of the first alternatives is the use of NIR microscopy (Infrared microscopy), which combines the advantages of microscopy and NIR. In 2004, the first study relating this problematic with Hyperspectral imaging was published [7] . Hyperspectral libraries are constructed, which are representative of the wide diversity of ingredients usually present in the preparation of compound feeds. These libraries can be used together with chemometric tools to investigate the limit of detection, specificity and reproducibility of the NIR hyperspectral imaging method for the detection and quantification of animal ingredient in feed.

Mineralogy

The original field of development for hyperspectral remote sensing, hyperspectral sensing of minerals is now well developed. Many minerals can be identified from images, and their relation to the presence of valuable minerals such as gold and diamonds is well understood. Currently the move is towards understanding the relation between oil and gas leakages from pipelines and natural wells; their effect on the vegetation and the spectral signatures. Recent work includes the PhD dissertations of Werff[8] and Noomen[9] .

Physics

Physicists use an electron microscopy technique that involves microanalysis using either Energy dispersive X-ray spectroscopy (EDS), Electron energy loss spectroscopy (EELS), Infrared Spectroscopy(IR), Raman Spectroscopy, or cathodoluminescence (CL) spectroscopy, in which the entire spectrum measured at each point is recorded. EELS hyperspectral imaging is performed in a scanning transmission electron microscope (STEM); EDS and CL mapping can be performed in STEM as well, or in a scanning electron microscope or electron probe microanalyzer (EPMA). Often, multiple techniques (EDS, EELS, CL) are used simultaneously.

In a "normal" mapping experiment, an image of the sample will be made that is simply the intensity of a particular emission mapped in an XY raster. For example, an EDS map could be made of a steel sample, in which iron x-ray intensity is used for the intensity grayscale of the image. Dark areas in the image would indicate not-iron-bearing impurities. This could potentially give misleading results; if the steel contained tungsten inclusions, for example, the high atomic number of tungsten could result in bremsstrahlung radiation that made the iron-free areas *appear* to be rich in iron.

By hyperspectral mapping, instead, the entire spectrum at each mapping point is acquired, and a quantitative analysis can be performed by computer post-processing of the data, and a quantitative map of iron content produced. This would show which areas contained no iron, despite the anomalous x-ray counts caused by bremsstrahlung. Because EELS core-loss edges are small signals on top of a large background, hyperspectral imaging allows large improvements to the quality of EELS chemical maps.

Similarly, in CL mapping, small shifts in the peak emission energy could be mapped, which would give information regarding slight chemical composition changes or changes in the stress state of a sample.

Surveillance

Hyperspectral surveillance is the implementation of hyperspectral scanning technology for surveillance purposes. Hyperspectral imaging is particularly useful in military surveillance because of measures that military entities now take to avoid airborne surveillance. Airborne surveillance has been in effect since soldiers used tethered balloons to spy on troops during the American Civil War, and since that time we have learned not only to hide from the naked eye, but to mask our heat signature to blend in to the surroundings and avoid infrared scanning, as well. The idea that drives hyperspectral surveillance is that hyperspectral scanning draws information from such a large portion of the light spectrum that any given object should have a unique spectral signature in at least a few of the many bands that get scanned.[1]

Advantages and disadvantages

The primary advantages to hyperspectral imaging is that, because an entire spectrum is acquired at each point, the operator needs no prior knowledge of the sample, and post-processing allows all available information from the dataset to be mined.

The primary disadvantages are cost and complexity. Fast computers, sensitive detectors, and large data storage capacities are needed for analyzing hyperspectral data. Significant data storage capacity is necessary since hyperspectral cubes are large multi-dimensional datasets, potentially exceeding hundreds of megabytes. All of these factors greatly increase the cost of acquiring and processing hyperspectral data. Also, one of the hurdles that researchers have had to face is finding ways to program hyperspectral satellites to sort through data on their own and transmit only the most important images, as both transmission and storage of that much data could prove difficult and costly.[1] As a relatively new analytical technique, the full potential of hyperspectral imaging has not yet been realized.

See also

- Airborne Real-time Cueing Hyperspectral Enhanced Reconnaissance
- Full Spectral Imaging
- Multi-spectral image
- Chemical imaging
- Remote Sensing
- Sensor fusion
- ERDAS IMAGINE
- Liquid Crystal Tunable Filter

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External links

- SpecTIR (http://www.spectir.com/) - Hyperspectral solutions and end to end global data collection & analysis
- Opticks (http://opticks.org/) - open source, remote sensing application and development framework.
- ITT Visual Information Solutions - ENVI Hyperspectral Image Processing Software (http://www.ittvis.com/ProductServices/ENVI.aspx)
- A Hyperspectral Imaging Prototype (http://www.inrim.it/res/hyperspectral_imaging/) Fourier transform spectroscopy is combined with Fabry-Perot interferometry
- Middleton Research (http://www.middletonresearch.com) Hyperspectral Imaging products, custom engineering solutions
- Photon etc. (http://photonetc.com/index.php?lan=en&sec=300&sub1=3000&sub2=1023) Hyperspectral Imaging Systems
- UmBio - Evince. Hyperspectral image analysis in real-time. Visual information solutions, see industrial demo movies (http://beta.umbio.com/Public files/Products/Evince Image/EvinceImage.aspx)
- A Matlab Hyperspectral Toolbox (http://matlabhyperspec.sourceforge.net/)
- Telops Hyper-Cam (http://www.hyper-cam.com/) Commercial infrared hyperspectral camera

Multi-spectral image

A **Multi-spectral image** is one that captures image data at specific frequencies across the electromagnetic spectrum. The wavelengths may be separated by filters or by the use of instruments that are sensitive to particular wavelengths, including light from frequencies beyond the visible light range, such as infrared. Multi-spectral imaging can allow extraction of additional information that the human eye fails to capture with its receptors for red, green and blue. It was originally developed for space-based imaging.

Multi-spectral images are the main type of images acquired by Remote sensing (RS) radiometers. Dividing the spectrum into many bands, multi-spectral is the opposite of panchromatic which records only the total intensity of radiation falling on each pixel. Usually satellites have 3 to 7 or more radiometers (Landsat has 7). Each one acquires one digital image (in remote sensing, called a *scene*) in a small band of visible spectra, ranging 0.7 μm to 0.4 μm, called red-green-blue (RGB) region, and going to infra-red wavelengths of 0.7 μm to 10 or more μm, classified as NIR-Near InfraRed, MIR-Middle InfraRed and FIR-Far InfraRed or Thermal. In the Landsat case the 7 scenes comprise a 7 band multi spectral image. Multispectral images with more numerous bands or finer spectral resolution or wider spectral coverage may be called "hyperspectral" or "ultra-spectral".

This technology has also assisted in the interpretation of ancient papyri such as those found at Herculaneum, by imaging the fragments in the infrared range (1000nm). Often the text on the documents appears to be as black ink on black paper to the naked eye. At 1000nm, the difference in light reflectivity makes the text clearly readable. It has also been used to image the Archimedes Palimpsest by imaging the parchment leaves in bandwidths from 365-870 nm and then using advanced digital image processing techniques to reveal the under text of Archimedes work.

The availability of wavelengths for remote sensing and imaging is limited by infrared window and optical window.

Spectral bands

The wavelengths are approximate; exact values depend on the particular satellite's instruments:

- **Blue**, 450-515..520 nm, used for atmospheric and deep water imaging. Can reach within 150 feet (46 m) deep in clear water.
- **Green**, 515..520-590..600 nm, used for imaging of vegetation and deep water structures, up to 90 feet (27 m) in clear water.
- **Red**, 600..630-680..690 nm, used for imaging of man-made objects, water up to 30 feet (9.1 m) deep, soil, and vegetation.
- **Near infrared**, 750-900 nm, primarily for imaging of vegetation.
- **Mid-infrared**, 1550-1750 nm, for imaging vegetation and soil moisture content, and some forest fires.
- **Mid-infrared**, 2080-2350 nm, for imaging soil, moisture, geological features, silicates, clays, and fires.
- **Thermal infrared**, 10400-12500 nm, uses emitted radiation instead of reflected, for imaging of geological structures, thermal differences in water currents, fires, and for night studies.
- **Radar** and related technologies, useful for mapping terrain and for detecting various objects.

Spectral band usage

For different purposes, different combinations of spectral bands can be used. They are usually represented with red, green, and blue channels. Mapping of bands to colors depends on the purpose of the image and the personal preferences of the analysts. Thermal infrared is often omitted from consideration due to poor spatial resolution, except for special purposes.

- **True-color**. Uses only red, green, and blue channels, mapped to their respective colors. A plain color photograph. Good for analyzing man-made objects. Easy to understand for beginner analysts.
- **Green-red-infrared**, where blue channel is replaced with near infrared. Vegetation, highly reflective in near IR, then shows as blue. This combination is often used for detection of vegetation and camouflage.
- **Blue-nearIR-midIR**, where blue channel uses visible blue, green uses near-infrared (so vegetation stays green), and mid-infrared is shown as red. Such images allow seeing the water depth, vegetation coverage, soil moisture content, and presence of fires, all in a single image.

Many other combinations are in use. Near infrared is often shown as red, making vegetation covered areas appear red.

Multispectral Data Analysis Software

- MicroMSI endorsed by the NGA.
- Opticks - an open source remote sensing application.

See also

- Hyperspectral imaging
- Full Spectral Imaging
- Remote sensing
- Spy satellite
- Imaging spectroscopy
- Imaging spectrometer
- Liquid Crystal Tunable Filter
- Satellite imagery

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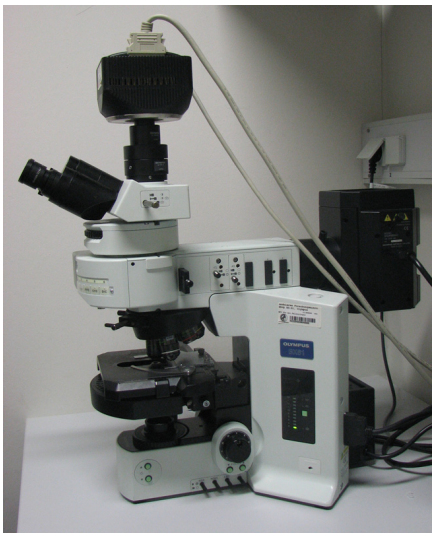
Fluorescence Imaging

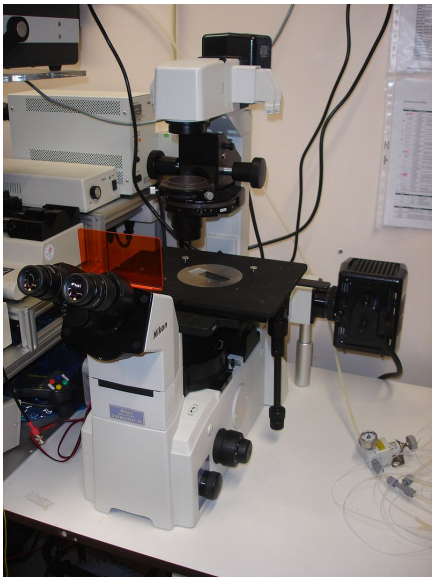
A **fluorescence microscope** (colloquially synonymous with *epifluorescence microscope*) is an optical microscope used to study properties of organic or inorganic substances using the phenomena of fluorescence and phosphorescence instead of, or in addition to, reflection and absorption.[1] [2]



An upright fluorescence microscope (Olympus BX61) with the fluorescent filter cube turret above the objective lenses, coupled with a digital camera.

Technique

In most cases, a component of interest in the specimen can be labeled specifically with a fluorescent molecule called a fluorophore (such as green fluorescent protein (GFP), fluorescein or DyLight 488).[1] The specimen is illuminated with light of a specific wavelength (or wavelengths) which is absorbed by the fluorophores, causing them to emit light of longer wavelengths (i.e. of a different color than the absorbed light). The illumination light is separated from the much weaker emitted fluorescence through the use of a spectral emission filter. Typical components of a fluorescence microscope are the light source (xenon arc lamp or mercury-vapor lamp), the excitation filter, the dichroic mirror (or dichromatic beamsplitter), and the emission filter (see figure below). The filters and the dichroic are chosen to match the spectral excitation and emission characteristics of the fluorophore used to label the specimen.[1] In this manner, the distribution of a single fluorophore (color) is imaged at a time. Multi-color images of several types of fluorophores must be composed by combining several single-color images.[1]

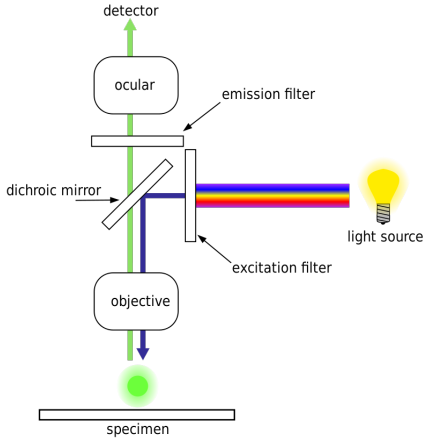


An inverted fluorescence microscope (Nikon TE2000) with the fluorescent filter cube turret below the stage. Note the orange plate that allows the user to look at a sample while protecting their eyes from the UV light.

Most fluorescence microscopes in use are epifluorescence microscopes (i.e. excitation and observation of the fluorescence are from above (*epi–*) the specimen). These microscopes have become an important part in the field of biology, opening the doors for more advanced microscope designs, such as the confocal microscope and the total internal reflection fluorescence microscope (TIRF).

Fluorophores lose their ability to fluoresce as they are illuminated in a process called photobleaching. Special care must be taken to prevent photobleaching through the use of more robust fluorophores, by minimizing illumination, or by introducing a scavenger system to reduce the rate of photobleaching.

Epifluorescence microscopy



Schematic of a fluorescence microscope.

Epifluorescence microscopy is a method of fluorescence microscopy that is widely used in life sciences. The excitatory light is passed from above (or, for inverted microscopes, from below), through the objective lens and then onto the specimen instead of passing it first through the specimen. The fluorescence in the specimen gives rise to emitted light which is focused to the detector by the same objective that is used for the excitation. Since most of the excitatory light is transmitted through the specimen, only reflected excitatory light reaches the objective together with the emitted light and this method therefore gives an improved signal to noise ratio. An additional filter between the objective and the detector can filter out the remaining excitation light from fluorescent light. A common use in biology is to apply fluorescent or fluorochrome stains to the specimen in order to image distributions of proteins or other molecules of interest.

Improvements and sub-diffraction techniques

The nature of light limits the size of the spot to which light can be focused. According to the diffraction limit a focused light distribution cannot be made smaller than approximately half of the wavelength of the used light. Uncovered in the 19th century by Ernst Abbe this has been a barrier of the achievable resolution of fluorescence light microscopes for a long time. While resolution is denoted by the ability to discern different objects of the same kind, localizing or tracking of single particles have been performed with a precision much below the diffraction limit.

Several improvements in microscopy techniques have been invented in the 20th century and have resulted in increased resolution and contrast to some extent. However they did not overcome the diffraction limit. In 1978 first theoretical ideas have been developed to break this barrier by using a 4Pi microscope as a confocal laser scanning fluorescence microscope where the light is focused ideally from all sides to a common focus which is used to scan the object by 'point-by-point' excitation combined with 'point-by-point' detection [3] . However, the first experimental demonstration of the 4pi microscope took place in 1994 [4] . The 4Pi microscopy is maximizing the amount of available focusing directions by using two opposing objective lenses or Multi-photon microscopy using redshifted light and multi-photon excitation.

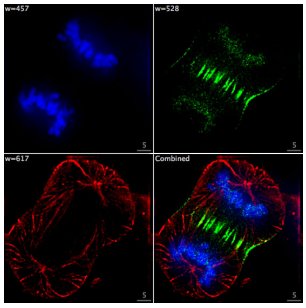
The first technique to really achieve a sub-diffraction resolution was STED microscopy, proposed in 1994. This method and all techniques following the RESOLFT concept rely on a strong non-linear interaction between light and fluorescing molecules. The molecules are driven strongly between distinguishable molecular states at each specific location, so that finally light can be emitted at only a small fraction of space, hence an increased resolution.

As well in the 1990ies another super resolution microscopy method based on wide field microscopy has been developed. Substantially improved size resolution of cellular nanostructures stained with a fluorescent marker was achieved by development of SPDM localization microscopy and the structured laser illumination (spatially modulated illumination, SMI) [5] . Combining the principle of SPDM with SMI resulted in the development of the Vertico SMI microscope [6] [7] . Single molecule detection of normal blinking fluorescent dyes like GFP can be achieved by using a further development of SPDM the so-called SPDMphymod technology which makes it possible

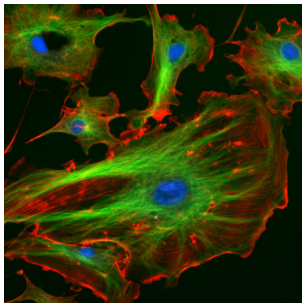
to detect and count two different fluorescent molecule types at the molecular level (this technology is referred to as 2CLM, 2 Color Localization Microscopy) [8] .

Alternatively, the advent of photoactivated localization microscopy could achieve similar results by relying on blinking or switching of single molecules, where the fraction of fluorescing molecules is very small at each time. This stochastic response of molecules on the applied light corresponds also to a highly nonlinear interaction, leading to subdiffraction resolution.

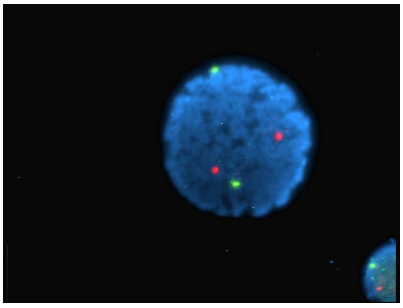
Gallery



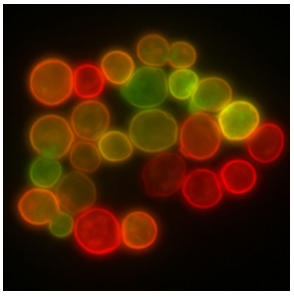
Epifluorescent imaging of the three components in a dividing human cancer cell. DNA is stained blue, a protein called INCENP is green, and the microtubules are red. Each fluorophore is imaged separately using a different combination of excitation and emission filters, and the images are captured sequentially using a digital CCD camera, then overlaid to give a complete image.



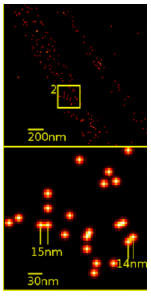
Endothelial cells under the microscope. Nuclei are stained blue with DAPI, microtubules are marked green by an antibody bound to FITC and actin filaments are labeled red with phalloidin bound to TRITC. Bovine pulmonary artery endothelial (BPAE) cells



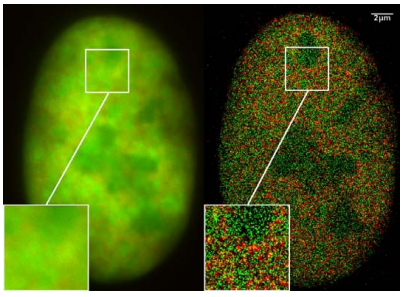
Human lymphocyte nucleus stained with DAPI with chromosome 13 (green) and 21 (red) centromere probes hybridized (Fluorescent in situ hybridization (FISH))



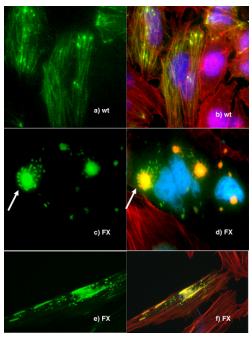
Yeast cell membrane visualized by some membrane proteins fused with RFP and GFP fluorescent markers. Imposition of light from both of markers results in yellow color.



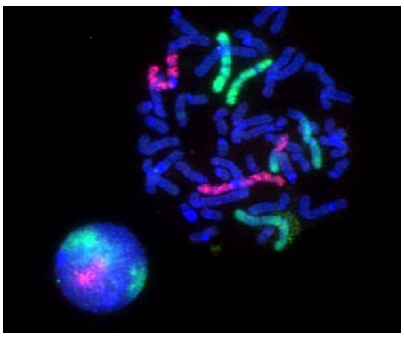
Super Resolution Microscopy: Single YFP molecule detection in a human cancer cell. Typical distance measurements in the 15 nm range (5 nm standard deviation) measured with a Vertico-SMI/SPDMphymod microscope



Super Resolution Microscopy: Co-localzation microscopy (2CLM) with GFP and RFP fusion proteins (nucleus of a bone cancer cell) 120.000 localized molecules in a wide-field area (470 μm^2) measured with a Vertico-SMI/SPDMphymod micrsocpe



Fluorescence microscopy of DNA Expression in the Human Wild-Type and P239S Mutant Palladin.



Fluorescence microscopy images of sun flares pathology in a blood cell showing the affected areas in red.

See also

- Microscope
- Mercury-vapor lamp, Xenon arc lamp
- Stokes shift

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External links

- Fluorophores.org (http://www.fluorophores.org) - Database of fluorescent dyes.

Fluorescence correlation spectroscopy

Fluorescence correlation spectroscopy (**FCS**) is a correlation analysis of fluctuation of the fluorescence intensity. The analysis provides parameters of the physics under the fluctuations. One of the interesting applications of this is an analysis of the concentration fluctuations of fluorescent particles (molecules) in solution. In this application, the fluorescence emitted from a very tiny space in solution containing a small number of fluorescent particles (molecules) is observed. The fluorescence intensity is fluctuating due to Brownian motion of the particles. In other words, the number of the particles in the sub-space defined by the optical system is randomly changing around the average number. The analysis gives the average number of fluorescent particles and average diffusion time, when the particle is passing through the space. Eventually, both the concentration and size of the particle (molecule) are determined. Since the method is observing a small number of molecule in a very tiny spot, it is a very sensitive analytical tool. Both parameters are very important and essential in the biochemical research, biophysics and chemistry. In contrast to the other method, such as HPLC analysis, this method has no physical separation process and has a good spatial resolution determined by the optics. These are of great advantage. Moreover, the method enables us to observe fluorescence-tagged molecules in the biochemical pathway in the intact living cells. Then, it opens a new area, "in situ or in vivo biochemistry", tracing biochemical pathway in the intact cells and organs.

Commonly, FCS is employed in the context of optical microscopy, in particular confocal or two-photon microscopy. In these techniques light is focused on a sample and the measured fluorescence intensity fluctuations (due to diffusion, physical or chemical reactions, aggregation, etc.) are analyzed using the temporal autocorrelation. Because the measured property is essentially related to the magnitude and/or the amount of fluctuations, there is an optimum measurement regime at the level when individual species enter or exit the observation volume (or turn on and off in the volume). When too many entities are measured at the same time the overall fluctuations are small in comparison to the total signal and may not be resolvable – in the other direction, if the individual fluctuation-events are too sparse in time, one measurement may take prohibitively too long. FCS is in a way the fluorescent counterpart to dynamic light scattering, which uses coherent light scattering, instead of (incoherent) fluorescence.

When an appropriate model is known, FCS can be used to obtain quantitative information such as

- diffusion coefficients
- hydrodynamic radii
- average concentrations
- kinetic chemical reaction rates
- singlet-triplet dynamics

Because fluorescent markers come in a variety of colors and can be specifically bound to a particular molecule (e.g. proteins, polymers, metal-complexes, etc.), it is possible to study the behavior of individual molecules (in rapid succession in composite solutions). With the development of sensitive detectors such as avalanche photodiodes the detection of the fluorescence signal coming from individual molecules in highly dilute samples has become practical. With this emerged the possibility to conduct FCS experiments in a wide variety of specimens, ranging from materials science to biology. The advent of engineered cells with genetically tagged proteins (like green fluorescent protein) has made FCS a common tool for studying molecular dynamics in living cells.

History

Signal-correlation techniques were first experimentally applied to fluorescence in 1972 by Magde, Elson, and Webb[1] , who are therefore commonly credited as the "inventors" of FCS. The technique was further developed in a group of papers by these and other authors soon after, establishing the theoretical foundations and types of applications.[2] [3] [4] See Thompson (1991)[5] for a review of that period.

Beginning in 1993[6] , a number of improvements in the measurement techniques—notably using confocal microscopy, and then two-photon microscopy—to better define the measurement volume and reject background—greatly improved the signal-to-noise ratio and allowed single molecule sensitivity.[7] [8] Since then, there has been a renewed interest in FCS, and as of August 2007 there have been over 3,000 papers using FCS found in Web of Science. See Krichevsky and Bonnet[9] for a recent review. In addition, there has been a flurry of activity extending FCS in various ways, for instance to laser scanning and spinning-disk confocal microscopy (from a stationary, single point measurement), in using cross-correlation (FCCS) between two fluorescent channels instead of autocorrelation, and in using Förster Resonance Energy Transfer (FRET) instead of fluorescence.

Typical FCS setup

The typical FCS setup consists of a laser line (wavelengths ranging typically from 405–633 nm (cw), and from 690–1100 nm (pulsed)), which is reflected into a microscope objective by a dichroic mirror. The laser beam is focused in the sample, which contains fluorescent particles (molecules) in such high dilution, that only a few are within the focal spot (usually 1–100 molecules in one fL). When the particles cross the focal volume, they fluoresce. This light is collected by the same objective and, because it is red-shifted with respect to the excitation light it passes the dichroic mirror reaching a detector, typically a photomultiplier tube or avalanche photodiode detector. The resulting electronic signal can be stored either directly as an intensity versus time trace to be analyzed at a later point, or computed to generate the autocorrelation directly (which requires special acquisition cards). The FCS curve by itself only represents a time-spectrum. Conclusions on physical phenomena have to be extracted from there with appropriate models. The parameters of interest are found after fitting the autocorrelation curve to modeled functional forms. [10]

The measurement volume

The measurement volume is a convolution of illumination (excitation) and detection geometries, which result from the optical elements involved. The resulting volume is described mathematically by the point spread function (or PSF), it is essentially the image of a point source. The PSF is often described as an ellipsoid (with unsharp boundaries) of few hundred nanometers in focus diameter, and almost one micrometre along the optical axis. The shape varies significantly (and has a large impact on the resulting FCS curves) depending on the quality of the optical elements (it is crucial to avoid astigmatism and to check the real shape of the PSF on the instrument). In the case of confocal microscopy, and for small pinholes (around one Airy unit), the PSF is well approximated by Gaussians:

$$PSF(r,z) = I_0 e^{-2r^2/\omega_{xy}^2} e^{-2z^2/\omega_z^2}$$

where I_0 is the peak intensity, r and z are radial and axial position, and ω_{xy} and ω_z are the radial and axial radii, and $\omega_z > \omega_{xy}$. This Gaussian form is assumed in deriving the functional form of the autocorrelation.

Typically ω_{xy} is 200–300 nm, and ω_z is **2–6** times larger.[11] One common way of calibrating the measurement volume parameters is to perform FCS on a species with known diffusion coefficient and concentration (see below). Diffusion coefficients for common fluorophores in water are given in a later section.

The Gaussian approximation works to varying degrees depending on the optical details, and corrections can sometimes be applied to offset the errors in approximation.[12]

Autocorrelation function

The (temporal) autocorrelation function is the correlation of a time series with itself shifted by time τ, as a function of τ:

$$G(\tau) = \frac{\langle \delta I(t) \delta I(t+\tau) \rangle}{\langle I(t) \rangle^2} = \frac{\langle I(t) I(t+\tau) \rangle}{\langle I(t) \rangle^2} - 1$$

where $\delta I(t) = I(t) - \langle I(t) \rangle$ is the deviation from the mean intensity. The normalization (denominator) here is the most commonly used for FCS, because then the correlation at $\tau =$ (), *G*(0), is related to the average number of particles in the measurement volume.

Interpreting the autocorrelation function

To extract quantities of interest, the autocorrelation data can be fitted, typically using a nonlinear least squares algorithm. The fit's functional form depends on the type of dynamics (and the optical geometry in question).

Normal diffusion

The fluorescent particles used in FCS are small and thus experience thermal motions in solution. The simplest FCS experiment is thus normal 3D diffusion, for which the autocorrelation is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D))(1 + a^{-2}(\tau/\tau_D))^{1/2}} + G(\infty)$$

where $a = \omega_z/\omega_{xy}$ is the ratio of axial to radial e^{-2}radii of the measurement volume, and τ_D is the characteristic residence time. This form was derived assuming a Gaussian measurement volume. Typically, the fit would have three free parameters--G(0), $G(\infty)$, and τ_D--from which the diffusion coefficient and fluorophore concentration can be obtained.
With the normalization used in the previous section, *G*(0) gives the mean number of diffusers in the volume <N>, or equivalently—with knowledge of the observation volume size—the mean concentration:

$$G(0) = \frac{1}{\langle N \rangle} = \frac{1}{V_{\text{eff}} \langle C \rangle},$$

where the effective volume is found from integrating the Gaussian form of the measurement volume and is given by:

$V_{\text{eff}} = \pi^{3/2} \omega_{xy}^2 \omega_z$.

τ_D gives the diffusion coefficient:

$D = \omega_{xy}^2 / 4\tau_D$.

Anomalous diffusion

If the diffusing particles are hindered by obstacles or pushed by a force (molecular motors, flow, etc.) the dynamics is often not sufficiently well-described by the normal diffusion model, where the mean squared displacement (MSD) grows linearly with time. Instead the diffusion may be better described as anomalous diffusion, where the temporal dependenc of the MSD is non-linear as in the power-law:

$$MSD = 6 D_a t^{\alpha}$$

where D_a is an anomalous diffusion coefficient. "Anomalous diffusion" commonly refers only to this very generic model, and not the many other possibilities that might be described as anomalous. Also, a power law is, in a strict sense, the expected form only for a narrow range of rigorously defined systems, for instance when the distribution of obstacles is fractal. Nonetheless a power law can be a useful approximation for a wider range of systems.
The FCS autocorrelation function for anomalous diffusion is:

$$G(\tau) = G(0)\frac{1}{(1+(\tau/\tau_D)^{\alpha})(1+a^{-2}(\tau/\tau_D)^{\alpha})^{1/2}} + G(\infty),$$

where the anomalous exponent α is the same as above, and becomes a free parameter in the fitting.

Using FCS, the anomalous exponent has been shown to be an indication of the degree of molecular crowding (it is less than one and smaller for greater degrees of crowding)[13].

Polydisperse diffusion

If there are diffusing particles with different sizes (diffusion coefficients), it is common to fit to a function that is the sum of single component forms:

$$G(\tau) = G(0)\sum_i \frac{\alpha_i}{(1+(\tau/\tau_{D,i}))(1+a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where the sum is over the number different sizes of particle, indexed by i, and α_i gives the weighting, which is related to the quantum yield and concentration of each type. This introduces new parameters, which makes the fitting more difficult as a higher dimensional space must be searched. Nonlinear least square fitting typically becomes unstable with even a small number of $\tau_{D,i}$s. A more robust fitting scheme, especially useful for polydisperse samples, is the Maximum Entropy Method[14].

Diffusion with flow

With diffusion together with a uniform flow with velocity v in the lateral direction, the autocorrelation is[15]:

where $\tau_v = \omega_{xy}/v$ is the average residence time if there is only a flow (no diffusion).

Chemical relaxation

A wide range of possible FCS experiments involve chemical reactions that continually fluctuate from equilibrium because of thermal motions (and then "relax"). In contrast to diffusion, which is also a relaxation process, the fluctuations cause changes between states of different energies. One very simple system showing chemical relaxation would be a stationary binding site in the measurement volume, where particles only produce signal when bound (e.g. by FRET, or if the diffusion time is much faster than the sampling interval). In this case the autocorrelation is:

$$G(\tau) = G(0)\exp(-\tau/\tau_B) + G(\infty)$$

where

$$\tau_B = (k_{\text{on}} + k_{\text{off}})^{-1}$$

is the relaxation time and depends on the reaction kinetics (on and off rates), and:

$$G(0) = \frac{1}{\langle N\rangle}\frac{k_{on}}{k_{off}} = \frac{1}{\langle N\rangle}K$$

is related to the equilibrium constant *K*.

Most systems with chemical relaxation also show measureable diffusion as well, and the autocorrelation function will depend on the details of the system. If the diffusion and chemical reaction are decoupled, the combined autocorrelation is the product of the chemical and diffusive autocorrelations.

Triplet state correction

The autocorrelations above assume that the fluctuations are not due to changes in the fluorescent properties of the particles. However, for the majority of (bio)organic fluorophores--e.g. green fluorescent protein, rhodamine, Cy3 and Alexa Fluor dyes--some fraction of illuminated particles are excited to a triplet state (or other non-radiative decaying states) and then do not emit photons for a characteristic relaxation time τ_F. Typically τ_F is on the order of microseconds, which is usually smaller than the dynamics of interest (e.g. τ_D) but large enough to be measured. A

multiplicative term is added to the autocorrelation account for the triplet state. For normal diffusion:

where F is the fraction of particles that have entered the triplet state and τ_F is the corresponding triplet state relaxation time. If the dynamics of interest are much slower than the triplet state relaxation, the short time component of the autocorrelation can simply be truncated and the triplet term is unnecessary.

Common fluorescent probes

The fluorescent species used in FCS is typically a biomolecule of interest that has been tagged with a fluorophore (using immunohistochemistry for instance), or is a naked fluorophore that is used to probe some environment of interest (e.g. the cytoskeleton of a cell). The following table gives diffusion coefficients of some common fluorophores in water at room temperature, and their excitation wavelengths.

Fluorescent dye	D (×10^{-10} m^2 s^{-1})	Excitation wavelength (nm)	Reference
Rhodamine 6G	2.8, 3.0, 4.14 ± 0.05 @ 25.00 °C	514	[16], [17], [18]
Rhodamine 110	2.7	488	[19]
Tetramethyl rhodamine	2.6	543	
Cy3	2.8	543	
Cy5	2.5, 3.7 ± 0.15 @ 25.00 °C	633	[20], [21]
carboxyfluorescein	3.2	488	
Alexa-488	1.96,4.35 @ 22.5±0.5 °C	488	[22] [23]
Atto655-maleimide	4.07 ± 0.1 @ 25.00 °C	663	[24]
Atto655-carboxylicacid	4.26 ± 0.08 @ 25.00 °C	663	[25]
2′, 7′-difluorofluorescein (Oregon Green488)	4.11 ± 0.06 @ 25.00 °C	498	[26]

Variations of FCS

FCS almost always refers to the single point, single channel, temporal autocorrelation measurement, although the term "fluorescence correlation spectroscopy" out of its historical scientific context implies no such restriction. FCS has been extended in a number of variations by different researchers, with each extension generating another name (usually an acronym).

Fluorescence cross-correlation spectroscopy (FCCS)

FCS is sometimes used to study molecular interactions using differences in diffusion times (e.g. the product of an association reaction will be larger and thus have larger diffusion times than the reactants individually); however, FCS is relatively insensitive to molecular mass as can be seen from the following equation relating molecular mass to the diffusion time of globular particles (e.g. proteins):

$$\tau_D = \frac{3\pi\omega_{xy}^2\eta}{2kT}(M)^{1/3}$$

where η is the viscosity of the sample and M is the molecular mass of the fluorescent species. In practice, the diffusion times need to be sufficiently different--a factor of at least **1.6**--which means the molecular masses must differ by a factor of **4**.[27] Dual color fluorescence cross-correlation spectroscopy (FCCS) measures interactions by cross-correlating two or more fluorescent channels (one channel for each reactant), which distinguishes interactions more sensitively than FCS, particularly when the mass change in the reaction is small.

Brightness analysis methods (N&B,[28] PCH,[29] FIDA,[30] Cumulant Analysis[31])

Fluorescence cross correlation spectroscopy overcomes the weak dependence of diffusion rate on molecular mass by looking at multicolor coincidence. What about homo-interactions? The solution lies in brightness analysis. These methods use the heterogeneity in the intensity distribution of fluorescence to measure the molecular brightness of different species in a sample. Since dimers will contain twice the number of fluorescent labels as monomers, their molecular brightness will be approximately double that of monomers. As a result, the relative brightness is sensitive a measure of oligomerization. The average molecular brightness ($\langle \epsilon \rangle$) is related to the variance (σ^2) and the average intensity ($\langle I \rangle$) as follows:[32]

$$\langle \varepsilon \rangle = \frac{\sigma^2 - \langle I \rangle}{\langle I \rangle} = \sum_i f_i \varepsilon_i$$

Here f_i and ϵ_i are the fractional intensity and molecular brigthness, respectively, of species i .

Two- and three- photon FCS excitation

Several advantages in both spatial resolution and minimizing photodamage/photobleaching in organic and/or biological samples are obtained by two-photon or three-photon excitation FCS[33] [34] [35] [36] [37] .

FRET-FCS

Another FCS based approach to studying molecular interactions uses fluorescence resonance energy transfer (FRET) instead of fluorescence, and is called FRET-FCS.[38] With FRET, there are two types of probes, as with FCCS; however, there is only one channel and light is only detected when the two probes are very close—close enough to ensure an interaction. The FRET signal is weaker than with fluorescence, but has the advantage that there is only signal during a reaction (aside from autofluorescence).

Image correlation spectroscopy (ICS)

When the motion is slow (in biology, for example, diffusion in a membrane), getting adequate statistics from a single-point FCS experiment may take a prohibitively long time. More data can be obtained by performing the experiment in multiple spatial points in parallel, using a laser scanning confocal microscope. This approach has been called Image Correlation Spectroscopy (ICS)[39] . The measurements can then be averaged together.

Another variation of ICS performs a spatial autocorrelation on images, which gives information about the concentration of particles[40] . The correlation is then averaged in time.

A natural extension of the temporal and spatial correlation versions is spatio-temporal ICS (STICS) [41] . In STICS there is no explicit averaging in space or time (only the averaging inherent in correlation). In systems with non-isotropic motion (e.g. directed flow, asymmetric diffusion), STICS can extract the directional information. A variation that is closely related to STICS (by the Fourier transform) is *k*-space Image Correlation Spectroscopy (kICS).[42]

There are cross-correlation versions of ICS as well.[39]

Scanning FCS variations

Some variations of FCS are only applicable to serial scanning laser microscopes. Image Correlation Spectroscopy and its variations all were implemented on a scanning confocal or scanning two photon microscope, but transfer to other microscopes, like a spinning disk confocal microscope. Raster ICS (RICS)[43] , and position sensitive FCS (PSFCS)[44] incorporate the time delay between parts of the image scan into the analysis. Also, low dimensional scans (e.g. a circular ring)[45] —only possible on a scanning system—can access time scales between single point and full image measurements. Scanning path has also been made to adaptively follow particles.[46]

Spinning disk FCS, and spatial mapping

Any of the image correlation spectroscopy methods can also be performed on a spinning disk confocal microscope, which in practice can obtain faster imaging speeds compared to a laser scanning confocal microscope. This approach has recently been applied to diffusion in a spatially varying complex environment, producing a pixel resolution map of a diffusion coefficient.[47] . The spatial mapping of diffusion with FCS has subsequently been extended to the TIRF system.[48] Spatial mapping of dynamics using correlation techniques had been applied before, but only at sparse points[49] or at coarse resolution[41] .

Total internal reflection FCS

Total internal reflection fluorescence (TIRF) is a microscopy approach that is only sensitive to a thin layer near the surface of a coverslip, which greatly minimizes background fluorscence. FCS has been extended to that type of microscope, and is called TIR-FCS[50] . Because the fluorescence intensity in TIRF falls off exponentially with distance from the coverslip (instead of as a Gaussian with a confocal), the autocorrelation function is different.

Other fluorescent dynamical approaches

There are two main non-correlation alternatives to FCS that are widely used to study the dynamics of fluorescent species.

Fluorescence recovery after photobleaching (FRAP)

In FRAP, a region is briefly exposed to intense light, irrecoverably photobleaching fluorophores, and the fluorescence recovery due to diffusion of nearby (non-bleached) fluorophores is imaged. A primary advantage of FRAP over FCS is the ease of interpreting qualitative experiments common in cell biology. Differences between cell lines, or regions of a cell, or before and after application of drug, can often be characterized by simple inspection of movies. FCS experiments require a level of processing and are more sensitive to potentially confounding influences like: rotational diffusion, vibrations, photobleaching, dependence on illumination and fluorescence color, inadequate statistics, etc. It is much easier to change the measurement volume in FRAP, which allows greater control. In practice, the volumes are typically larger than in FCS. While FRAP experiments are typically more qualitative, some researchers are studying FRAP quantitatively and including binding dynamics.[51] A disadvantage of FRAP in cell biology is the free radical perturbation of the cell caused by the photobleaching. It is also less versatile, as it cannot measure concentration or rotational diffusion, or co-localization. FRAP requires a significantly higher concentration of fluorophores than FCS.

Particle tracking

In particle tracking, the trajectories of a set of particles are measured, typically by applying particle tracking algorithms to movies.[52] Particle tracking has the advantage that all the dynamical information is maintained in the measurement, unlike FCS where correlation averages the dynamics to a single smooth curve. The advantage is apparent in systems showing complex diffusion, where directly computing the mean squared displacement allows straightforward comparison to normal or power law diffusion. To apply particle tracking, the particles have to be distinguishable and thus at lower concentration than required of FCS. Also, particle tracking is more sensitive to noise, which can sometimes affect the results unpredictably.

See also

- Confocal microscopy
- Fluorescence cross-correlation spectroscopy,FCCS
- FRET
- Dynamic light scattering
- Diffusion coefficient

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External links

- Single-molecule spectroscopic methods (http://dx.doi.org/10.1016/j.sbi.2004.09.004)
- FCS Classroom (http://www.fcsxpert.com/classroom)
- Stowers Institute FCS Tutorial (http://research.stowers-institute.org/microscopy/external/Technology/FCS/index.htm)
- Cell Migration Consortium FCS Tutorial (http://www.cellmigration.org/resource/imaging/imaging_approaches_correlation_microscopy.shtml)

Fluorescence cross-correlation spectroscopy

Fluorescence cross-correlation spectroscopy (FCCS) was introduced by Eigen and Rigler in 1994 and experimentally realized by Schwille in 1997. It extends the fluorescence correlation spectroscopy (FCS) procedure by introducing high sensitivity for distinguishing fluorescent particles which have a similar diffusion coefficient. FCCS uses two species which are independently labelled with two spectrally separated fluorescent probes. These fluorescent probes are excited and detected by two different laser light sources and detectors commonly known as green and red respectively. Both laser light beams are focused into the sample and tuned so that they overlap to form a superimposed confocal observation volume.

The normalized cross-correlation function is defined for two fluorescent species G and R which are independent green, G and red, R channels as follows:

where differential fluorescent signals δI_G at a specific time, t and δI_R at a delay time, τ later is correlated with each other.

Modeling

Cross-correlation curves are modeled according to a slightly more complicated mathematical function than applied in FCS. First of all, the effective superimposed observation volume in which the G and R channels form a single observation volume, $V_{eff,RG}$ in the solution:

$$V_{eff,RG} = \pi^{3/2}(\omega_{xy,G}^2 + \omega_{xy,R}^2)(\omega_{z,G}^2 + \omega_{z,R}^2)^{1/2}/2^{3/2}$$

where $\omega_{xy,G}^2$ and $\omega_{xy,R}^2$ are radial parameters and $\omega_{z,G}$ and $\omega_{z,R}$ are the axial parameters for the G and R channels respectively.
The diffusion time, $\tau_{D,GR}$ for a doubly (G and R) fluorescent species is therefore described as follows:

$$\tau_{D,GR} = \frac{\omega_{xy,G}^2 + \omega_{xy,R}^2}{8D_{GR}}$$

where D_{GR} is the diffusion coefficient of the doubly fluorescent particle.

The cross-correlation curve generated from diffusing doubly labelled fluorescent particles can be modelled in separate channels as follows:

$$G_G(\tau) = 1 + \frac{(< C_G > Diff_k(\tau) + < C_{GR} > Diff_k(\tau))}{V_{eff,GR}(< C_G > + < C_{GR} >)^2}$$

$$G_R(\tau) = 1 + \frac{(< C_R > Diff_k(\tau) + < C_{GR} > Diff_k(\tau))}{V_{eff,GR}(< C_R > + < C_{GR} >)^2}$$

In the ideal case, the cross-correlation function is proportional to the concentration of the doubly labeled fluorescent complex:

with $Diff_k(\tau) = \frac{1}{(1+\frac{\tau}{\tau_{D,i}})(1+a^{-2}(\frac{\tau}{\tau_{D,i}})^{1/2}}$

Contrary to FCS, the intercept of the cross-correlation curve does not yield information about the doubly labelled fluorescent particles in solution.

See also

- Fluorescence correlation spectroscopy
- Dynamic light scattering
- Fluorescence spectroscopy
- Diffusion coefficient

External links

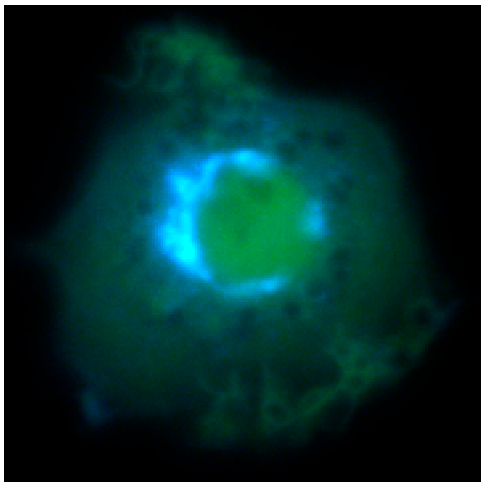
- FCS Classroom [1]

References

[1] http://www.fcsxpert.com/classroom

Förster resonance energy transfer

Förster resonance energy transfer (abbreviated **FRET**), also known as **fluorescence resonance energy transfer**, **resonance energy transfer** (**RET**) or **electronic energy transfer** (**EET**), is a mechanism describing energy transfer between two chromophores.



Fluorescently-labeled guanosine 5'-triphosphate hydrolase ARF reveals the protein's localization in the Golgi apparatus of a living macrophage. FRET studies revealed ARF activation in the Golgi and in the formation of phagosomes.[1]

A donor chromophore, initially in its electronic excited state, may transfer energy to an acceptor chromophore (in proximity, typically less than 10 nm) through nonradiative dipole–dipole coupling. This mechanism is termed "Förster resonance energy transfer" and is named after the German scientist Theodor Förster.[2] When both chromophores are fluorescent, the term "fluorescence resonance energy transfer" is often used instead, although the energy is not actually transferred by fluorescence.[3] ,[4] In order to avoid an erroneous interpretation of the phenomenon that (even when occurring between two fluorescent chromophores) is always a nonradiative transfer of energy, the name "Förster resonance energy transfer" is preferred to "fluorescence resonance energy transfer" – although the latter enjoys common usage in scientific literature, despite being incorrect. FRET is analogous to near field communication, in that the radius of interaction is much smaller than the

wavelength of light emitted. In the near field region, the excited chromophore emits a virtual photon that is instantly absorbed by a receiving chromophore. These virtual photons are undetectable, since their existence violates the conservation of energy and momentum, and hence FRET is known as a *radiationless* mechanism. From quantum electrodynamical calculations, it is determined that radiationless (FRET) and radiative energy transfer are the short- and long-range asymptotes of a single unified mechanism.[5] ,[6]

Theoretical basis

The FRET efficiency (E) is the quantum yield of the energy transfer transition, *i.e.* the fraction of energy transfer event occurring per donor excitation event:

$$E = \frac{k_{ET}}{k_f + k_{ET} + \sum k_i}$$

where k_{ET} is the rate of energy transfer, k_f the radiative decay rate and the k_i are the rate constants of any other de-excitation pathway.

The FRET efficiency depends on many parameters that can be grouped as follows:

- The distance between the donor and the acceptor
- The spectral overlap of the donor emission spectrum and the acceptor absorption spectrum.
- The relative orientation of the donor emission dipole moment and the acceptor absorption dipole moment.

E depends on the donor-to-acceptor separation distance r with an inverse 6th power law due to the dipole-dipole coupling mechanism:

$$E = \frac{1}{1 + (r/R_0)^6}$$

with R_0 being the Förster distance of this pair of donor and acceptor, i.e. the distance at which the energy transfer efficiency is 50%. The Förster distance depends on the overlap integral of the donor emission spectrum with the acceptor absorption spectrum and their mutual molecular orientation as expressed by the following equation:

$${R_0}^6 = \frac{9\,Q_0\,(\ln 10)\kappa^2\,J}{128\,\pi^5\,n^4\,N_A}$$

where Q_0 is the fluorescence quantum yield of the donor in the absence of the acceptor, κ^2 is the dipole orientation factor, n is the refractive index of the medium, N_A is Avogadro's number, and J is the spectral overlap integral calculated as

$$J = \int f_{\mathrm{D}}(\lambda)\,\epsilon_{\mathrm{A}}(\lambda)\,\lambda^4\,d\lambda$$

where f_{D} is the normalized donor emission spectrum, and ϵ_{A} is the acceptor molar extinction coefficient. κ^2 =2/3 is often assumed. This value is obtained when both dyes are freely rotating and can be considered to be isotropically oriented during the excited state lifetime. If either dye is fixed or not free to rotate, then κ^2 =2/3 will not be a valid assumption. In most cases, however, even modest reorientation of the dyes results in enough orientational averaging that κ^2 = 2/3 does not result in a large error in the estimated energy transfer distance due to the sixth power dependence of R_0 on κ^2. Even when κ^2 is quite different from 2/3 the error can be associated with a shift in R_0 and thus determinations of changes in relative distance for a particular system are still valid. Fluorescent proteins do not reorient on a timescale that is faster than their fluorescence lifetime. In this case $0 \le \kappa^2 \le 4$.

The FRET efficiency relates to the quantum yield and the fluorescence lifetime of the donor molecule as follows:

$$E = 1 - \tau'_{\mathrm{D}}/\tau_{\mathrm{D}}$$

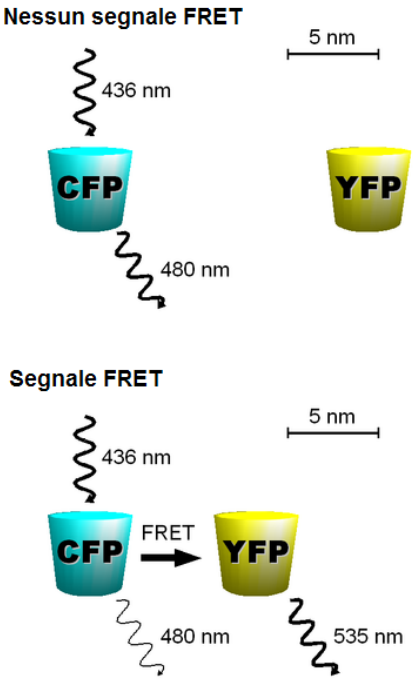
where τ'_{D} and τ_{D} are the donor fluorescence lifetimes in the presence and absence of an acceptor, respectively, or as

$$E = 1 - F'_{\mathrm{D}}/F_{\mathrm{D}}$$

where F'_{D} and F_{D} are the donor fluorescence intensities with and without an acceptor, respectively.

Methods

In fluorescence microscopy, fluorescence confocal laser scanning microscopy, as well as in molecular biology, FRET is a useful tool to quantify molecular dynamics in biophysics and biochemistry, such as protein-protein interactions, protein-DNA interactions, and protein conformational changes. For monitoring the complex formation between two molecules, one of them is labeled with a donor and the other with an acceptor, and these fluorophore-labeled molecules are mixed. When they are dissociated, the donor emission is detected upon the donor excitation. On the other hand, when the donor and acceptor are in proximity (1-10 nm) due to the interaction of the two molecules, the acceptor emission is predominantly observed because of the intermolecular FRET from the donor to the acceptor. For monitoring protein conformational changes, the target protein is labeled with a donor and an acceptor at two loci. When a twist or bend of the protein brings the change in the distance or relative orientation of the donor and acceptor, FRET change is observed. If a molecular interaction or a protein conformational change is dependent on ligand binding, this FRET technique is applicable to fluorescent indicators for the ligand detection.



Example of FRET between CFP and YFP (Wavelength vs. Absorption): a fusion protein containing CFP and YFP excited at 440nm wavelength. The fluorescent emission peak of CFP overlaps the excitation peak of YFP. Because the two proteins are adjacent to each other, the energy transfer is significant–a large proportion of the energy from CFP is transferred to YFP and creates a much larger YFP emission peak.

FRET studies are scalable: the extent of energy transfer is often quantified from the milliliter scale of cuvette-based experiments to the femtoliter scale of microscopy-based experiments. This quantification can be based directly (sensitized emission method) on detecting two emission channels under two different excitation conditions (primarily donor and primarily acceptor). However, for robustness reasons, FRET quantification is most often based on measuring changes in fluorescence intensity or fluorescence lifetime upon changing the experimental conditions (e.g. a microscope image of donor emission is taken with the acceptor being present. The acceptor is then bleached, such that it is incapable of accepting energy transfer and another donor emission image is acquired. A pixel-based quantification using the second equation in the theory section above is then possible.) An alternative way of temporarily deactivating the acceptor is based on its fluorescence saturation. Exploiting polarisation characteristics of light, a FRET quantification is also possible with only a single camera exposure.

CFP-YFP pairs

The most popular FRET pair for biological use is a cyan fluorescent protein (**CFP**) - yellow fluorescent protein (**YFP**) pair. Both are color variants of green fluorescent protein (**GFP**). While labeling with organic fluorescent dyes requires troublesome processes of purification, chemical modification, and intracellular injection of a host protein, GFP variants can be easily attached to a host protein by genetic engineering. By virtue of GFP variants, the use of FRET techniques for biological research is becoming more and more popular.

BRET

A limitation of FRET is the requirement for external illumination to initiate the fluorescence transfer, which can lead to background noise in the results from direct excitation of the acceptor or to photobleaching. To avoid this drawback, Bioluminescence Resonance Energy Transfer (or **BRET**) has been developed. This technique uses a bioluminescent luciferase (typically the luciferase from *Renilla reniformis*) rather than CFP to produce an initial photon emission compatible with YFP.

FRET and BRET are also the common tools in the study of biochemical reaction kinetics and molecular motors.

Photobleaching FRET

FRET efficiencies can also be inferred from the photobleaching rates of the donor in the presence and absence of an acceptor. This method can be performed on most fluorescence microscopes; one simply shines the excitation light (of a frequency that will excite the donor but not the acceptor significantly) on specimens with and without the acceptor fluorophore and monitors the donor fluorescence (typically separated from acceptor fluorescence using a bandpass filter) over time. The timescale is that of photobleaching, which is seconds to minutes, with fluorescence in each curve being given by

$$(\text{background}) + (\text{constant}) * e^{-(\text{time})/\tau_{\text{pb}}}$$

where $\tau_{\text{pb}}$is the photobleaching decay time constant and depends on whether the acceptor is present or not. Since photobleaching consists in the permanent inactivation of excited fluorophores, resonance energy transfer from an excited donor to an acceptor fluorophore prevents the photobleaching of that donor fluorophore, and thus high FRET efficiency leads to a longer photobleaching decay time constant:

$$E = 1 - \tau_{\text{pb}}/\tau'_{\text{pb}}$$

where $\tau'_{\text{pb}}$and $\tau_{\text{pb}}$are the photobleaching decay time constants of the donor in the presence and in the absence of the acceptor, respectively. (Notice that the fraction is the reciprocal of that used for lifetime measurements).
This technique was introduced by Jovin in 1989.[7] Its use of an entire curve of points to extract the time constants can give it accuracy advantages over the other methods. Also, the fact that time measurements are over seconds rather than nanoseconds makes it easier than fluorescence lifetime measurements, and because photobleaching decay rates do not generally depend on donor concentration (unless acceptor saturation is an issue), the careful control of concentrations needed for intensity measurements is not needed. It is, however, important to keep the illumination the same for the with- and without-acceptor measurements, as photobleaching increases markedly with more intense incident light.

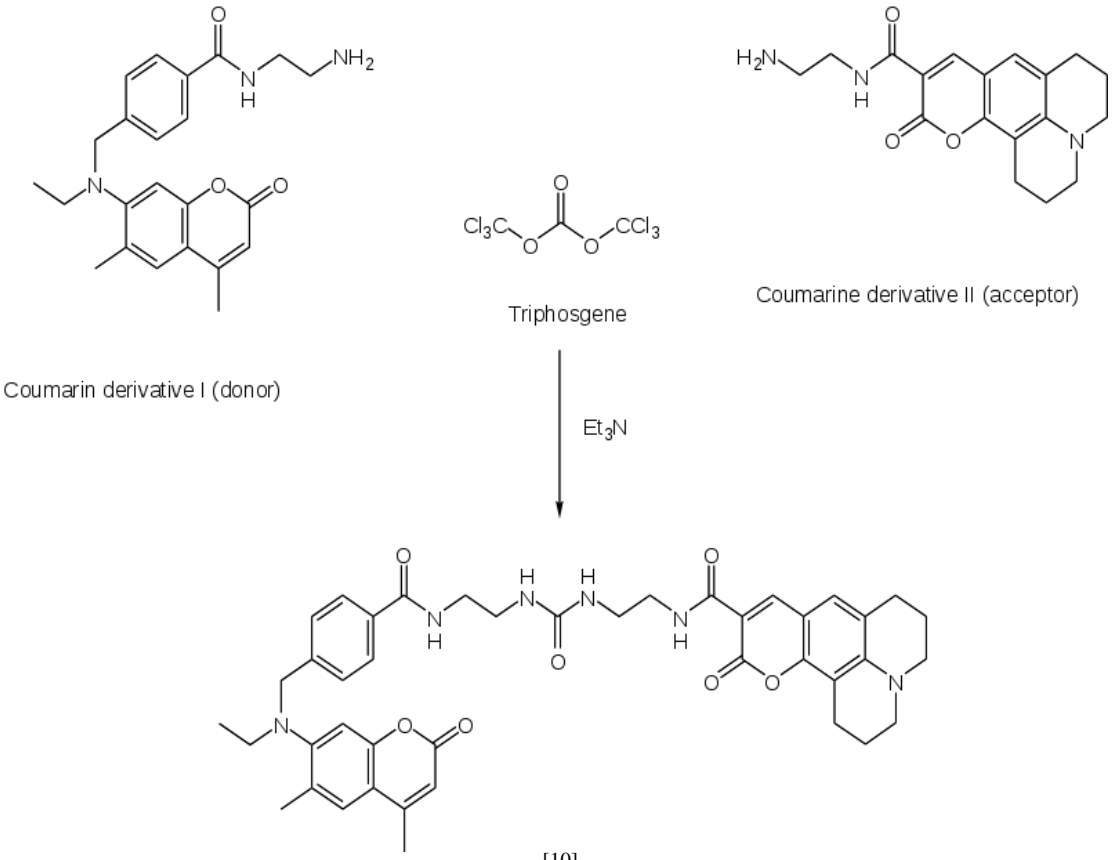
Other methods

A different, but related, mechanism is Dexter Electron Transfer.

An alternative method to detecting protein-protein proximity is the bimolecular fluorescence complementation (BiFC) where two halves of a YFP are fused to a protein. When these two halves meet they form a fluorophore after about 60 s - 1 hr.[8]

Applications

FRET has been applied in an experimental method for the detection of phosgene. In it, phosgene or rather triphosgene as a safe substitute serves as a linker between an acceptor and a donor coumarine (forming urea groups).[9] The presence of phosgene is detected at 5×10^{-5}M with a typical FRET emission at 464 nm.



FRET is also used to study lipid rafts in cell membranes.[10]

See also

- Resonant energy transfer is used for remotely powering equipment such as smart cards
- Fluorescence principles / energy transfer (FRET): light emitted upon excitation by illumination at a shorter wavelength
- Bioluminescence principles / energy transfer (BRET): light emitted by a chemical enzymatic reaction (Luminol/Peroxidase, Luciferin/Luciferase, Coelenterazine/Aequorin)
- FCS

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Further reading

- doi:10.1016/S0959-440X(00)00190-1 Recent advances in FRET: distance determination in protein–DNA complexes. *Current Opinion in Structural Biology* **2001**, *11(2)*, 201-207

External links

- Browser-based calculator to find the critical distance and FRET efficiency with known spectral overlap (http://www.calctool.org/CALC/chem/photochemistry/fret)
- FRET description (http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fret.htm)
- Fluorescence Resonance Energy Transfer (FRET) Microscopy (http://www.olympusmicro.com/primer/techniques/fluorescence/fret/fretintro.html)
- Lambert Instruments (http://www.lambert-instruments.com/)

X-ray microscope

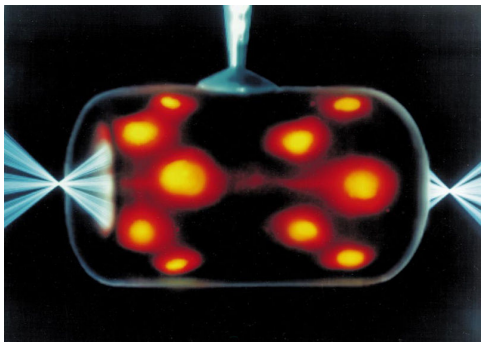
An **X-ray microscope** uses electromagnetic radiation in the soft X-ray band to produce images of very small objects.

Unlike visible light, X-rays do not reflect or refract easily, and they are invisible to the human eye. Therefore the basic process of an X-ray microscope is to expose film or use a charge-coupled device (CCD) detector to detect X-rays that pass through the specimen. It is a contrast imaging technology using the difference in absorption of soft x-ray in the water window region (wavelength region: 2.3 - 4.4 nm, photon energy region: 0.28 - 0.53 keV) by the carbon atom (main element composing the living cell) and the oxygen atom (main element for water).

Early X-ray microscopes by Paul Kirkpatrick and Albert Baez used grazing-incidence reflective optics to focus the X-rays, which grazed X-rays off parabolic curved mirrors at a very high angle of incidence. An alternative method of focusing X-rays is to use a tiny fresnel zone plate of concentric gold or nickel rings on a silicon dioxide substrate. Sir Lawrence Bragg produced some of the first usable X-ray images with his apparatus in the late 1940's.

In the 1950's Newberry produced a shadow X-ray microscope which placed the specimen between the source and a target plate, this became the basis for the first commercial X-ray microscopes from the General Electric Company.

The Advanced Light Source (ALS)[1] in Berkeley CA is home to XM-1 (http://www.cxro.lbl.gov/BL612/), a full field soft X-ray microscope operated by the Center for X-ray Optics [2] and dedicated to various applications in modern nanoscience, such as nanomagnetic materials, environmental and materials sciences and biology. XM-1 uses an X-ray lens to focus X-rays on a CCD, in a manner similar to an optical microscope. XM-1 still holds the world record in spatial resolution with Fresnel zone plates down to 15nm and is able to combine high spatial resolution with a sub-100ps time resolution to study e.g. ultrafast spin dynamics.



Indirect drive laser inertial confinement fusion uses a "hohlraum" which is irradiated with laser beam cones from either side on it its inner surface to bathe a fusion microcapsule inside with smooth high intensity X-rays. The highest energy X-rays which penetrate the hohlraum can be visualized using an X-ray microscope such as here, where X-radiation is represented in orange/red.

The ALS is also home to the world's first soft x-ray microscope designed for biological and biomedical research. This new instrument, XM-2 was designed and built by scientists from the National Center for X-ray Tomography (http://ncxt.lbl.gov).XM-2 is capable of producing 3-Dimensional tomograms of cells.

Sources of soft X-rays suitable for microscopy, such as synchrotron radiation sources, have fairly low brightness of the required wavelengths, so an alternative method of image formation is scanning transmission soft X-ray microscopy. Here the X-rays are focused to a point and the sample is mechanically scanned through the produced focal spot. At each point the transmitted X-rays are recorded with a detector such as a proportional counter or an avalanche photodiode. This type of Scanning Transmission X-ray Microscope (STXM) was first developed by researchers at Stony Brook University and was employed at the National Synchrotron Light Source at Brookhaven National Laboratory.

The resolution of X-ray microscopy lies between that of the optical microscope and the electron microscope. It has an advantage over conventional electron microscopy in that it can view biological samples in their natural state. Electron microscopy is widely used to obtain images with nanometer level resolution but the relatively thick living cell cannot be observed as the sample has to be chemically fixed, dehydrated, embedded in resin, then sliced ultra thin. However, it should be mentioned that cryo-electron microscopy allows the observation of biological specimens in their hydrated natural state, albeit embedded in water ice. Until now, resolutions of 30 nanometer are possible using the Fresnel zone plate lens which forms the image using the soft x-rays emitted from a synchrotron. Recently, more researchers have begun to use the soft x-rays emitted from laser-produced plasma rather than synchrotron radiation.

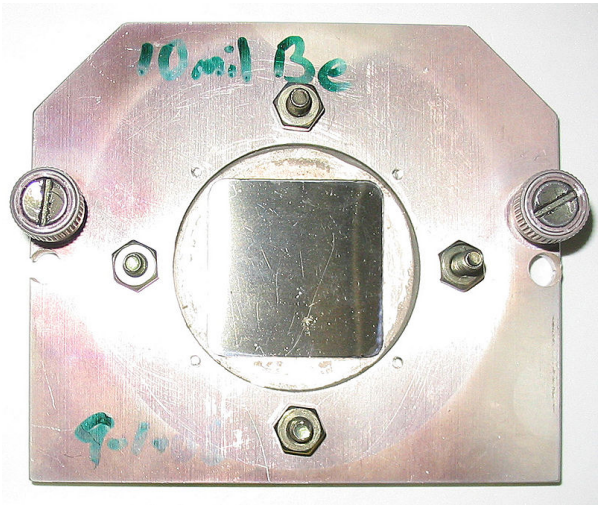
Additionally, X-rays cause fluorescence in most materials, and these emissions can be analyzed to determine the chemical elements of an imaged object. Another use is to generate diffraction patterns, a process used in X-ray crystallography. By analyzing the internal reflections of a diffraction pattern (usually with a computer program), the three-dimensional structure of a crystal can be determined down to the placement of individual atoms within its molecules. X-ray microscopes are sometimes used for these analyses because the samples are too small to be analyzed in any other way.

See also

- Synchrotron X-ray tomographic microscopy

External links

- Application of X-ray microscopy in analysis of living hydrated cells [3]
- Hard X-ray microbeam experiments with a sputtered-sliced Fresnel zone plate and its applications [4]
- Scientific applications of soft x-ray microscopy [5]



A square beryllium foil mounted in a steel case to be used as a window between a vacuum chamber and an X-ray microscope. Beryllium, due to its low Z number is highly transparent to X-rays.

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[3] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938
[4] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11972376
[5] http://www.cxro.lbl.gov/BL612/index.php?content=research.html

Electron Microscope

An **electron microscope** is a type of microscope that produces an electronically-magnified image of a specimen for detailed observation. The electron microscope (EM) uses a particle beam of electrons to illuminate the specimen and create a magnified image of it. The microscope has a greater resolving power than a light-powered optical microscope, because it uses electrons that have wavelengths about 100,000 times shorter than visible light (photons), and can achieve magnifications of up to 2,000,000x, whereas light microscopes are limited to 2000x magnification.

The electron microscope uses electrostatic and electromagnetic "lenses" to control the electron beam and focus it to form an image. These lenses are analogous to, but different from the glass lenses of an optical microscope that form a magnified image by focusing light on or through the specimen.

Electron microscopes are used to observe a wide range of biological and inorganic specimens including microorganisms, cells, large molecules, biopsy samples, metals, and crystals. Industrially, the electron microscope is primarily used for quality control and failure analysis in semiconductor device fabrication.

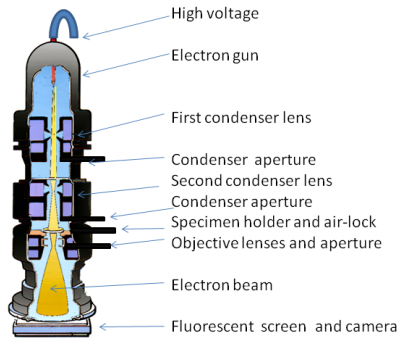


Diagram of a transmission electron microscope

A 1973 Siemens electron microscope, Musée des Arts et Métiers, Paris

History

In 1931, the German physicist Ernst Ruska and German electrical engineer Max Knoll constructed the prototype electron microscope, capable of four-hundred-power magnification; the apparatus was a practical application of the principles of electron microscopy.[1] Two years later, in 1933, Ruska built an electron microscope that exceeded the resolution attainable with an optical (lens) microscope.[1] Moreover, Reinhold Rudenberg, the scientific director of Siemens-Schuckertwerke, obtained the patent for the electron microscope in May 1931. Family illness compelled the electrical engineer to devise an electrostatic microscope, because he wanted to make visible the poliomyelitis virus.

Electron microscope constructed by Ernst Ruska in 1933

In 1937, the Siemens company financed the development work of Ernst Ruska and Bodo von Borries, and employed Helmut Ruska (Ernst's brother) to develop applications for the microscope, especially with biologic specimens.[1] [2] Also in 1937, Manfred von Ardenne pioneered the scanning electron microscope.[3] The first *practical* electron microscope was constructed in 1938, at the University of Toronto, by Eli Franklin Burton and students Cecil Hall, James Hillier, and Albert Prebus; and Siemens produced the first *commercial* Transmission Electron Microscope (TEM) in 1939.[4] Although contemporary electron microscopes are capable of two million-power magnification, as scientific instruments, they remain based upon Ruska's prototype.

Types

Transmission electron microscope (TEM)

The original form of electron microscope, the transmission electron microscope (TEM) uses a high voltage electron beam to create an image. The electrons are emitted by an electron gun, commonly fitted with a tungsten filament cathode as the electron source. The electron beam is accelerated by an anode typically at +100 keV (40 to 400 keV) with respect to the cathode, focused by electrostatic and electromagnetic lenses, and transmitted through the specimen that is in part transparent to electrons and in part scatters them out of the beam. When it emerges from the specimen, the electron beam carries information about the structure of the specimen that is magnified by the objective lens system of the microscope. The spatial variation in this information (the "image") is viewed by projecting the magnified electron image onto a fluorescent viewing screen coated with a phosphor or scintillator material such as zinc sulfide. The image can be photographically recorded by exposing a photographic film or plate directly to the electron beam, or a high-resolution phosphor may be coupled by means of a lens optical system or a fibre optic light-guide to the sensor of a CCD (charge-coupled device) camera. The image detected by the CCD may be displayed on a monitor or computer.

Resolution of the TEM is limited primarily by spherical aberration, but a new generation of aberration correctors have been able to partially overcome spherical aberration to increase resolution. Hardware correction of spherical aberration for the High Resolution TEM (HRTEM) has allowed the production of images with resolution below 0.5 Ångström (50 picometres)[5] at magnifications above 50 million times.[6] The ability to determine the positions of atoms within materials has made the HRTEM an important tool for nano-technologies research and development.[7]

Scanning electron microscope (SEM)

Unlike the TEM, where electrons of the high voltage beam carry the image of the specimen, the electron beam of the Scanning Electron Microscope (SEM)[8] does not at any time carry a complete image of the specimen. The SEM produces images by probing the specimen with a focused electron beam that is scanned across a rectangular area of the specimen (raster scanning). At each point on the specimen the incident electron beam loses some energy, and that lost energy is converted into other forms, such as heat, emission of low-energy secondary electrons, light emission (cathodoluminescence) or x-ray emission. The display of the SEM maps the varying intensity of any of these signals into the image in a position corresponding to the position of the beam on the specimen when the signal was generated. In the SEM image of an ant shown at right, the image was constructed from signals produced by a secondary electron detector, the normal or conventional imaging mode in most SEMs.

An image of an ant in a scanning electron microscope

Generally, the image resolution of an SEM is about an order of magnitude poorer than that of a TEM. However, because the SEM image relies on surface processes rather than transmission, it is able to image bulk samples up to many centimetres in size and (depending on instrument design and settings) has a great depth of field, and so can produce images that are good representations of the three-dimensional shape of the sample.

Reflection electron microscope (REM)

In the **Reflection Electron Microscope** (REM) as in the TEM, an electron beam is incident on a surface, but instead of using the transmission (TEM) or secondary electrons (SEM), the reflected beam of elastically scattered electrons is detected. This technique is typically coupled with Reflection High Energy Electron Diffraction (RHEED) and *Reflection high-energy loss spectrum (RHELS)*. Another variation is Spin-Polarized Low-Energy Electron Microscopy (SPLEEM), which is used for looking at the microstructure of magnetic domains.[9]

Scanning transmission electron microscope (STEM)

The STEM rasters a focused incident probe across a specimen that (as with the TEM) has been thinned to facilitate detection of electrons scattered *through* the specimen. The high resolution of the TEM is thus possible in STEM. The focusing action (and aberrations) occur before the electrons hit the specimen in the STEM, but afterward in the TEM. The STEMs use of SEM-like beam rastering simplifies annular dark-field imaging, and other analytical techniques, but also means that image data is acquired in serial rather than in parallel fashion.

Low voltage electron microscope (LVEM)

The low voltage electron microscope (LVEM) is a combination of SEM, TEM and STEM in one instrument, which operates at relatively low electron accelerating voltage of 5 kV. Low voltage increases image contrast which is especially important for biological specimens. This increase in contrast significantly reduces, or even eliminates the need to stain. Sectioned samples generally need to be thinner than they would be for conventional TEM (20-65 nm). Resolutions of a few nm are possible in TEM, SEM and STEM modes.[10] [11]

Sample preparation

Materials to be viewed under an electron microscope may require processing to produce a suitable sample. The technique required varies depending on the specimen and the analysis required:

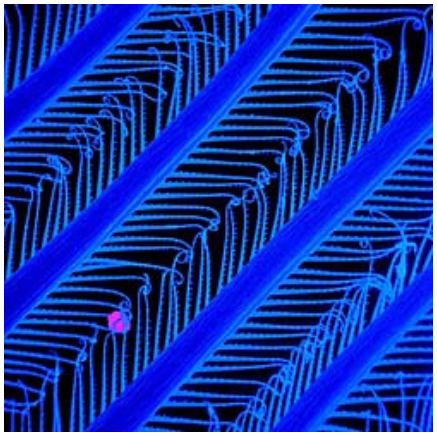
An insect coated in gold for viewing with a scanning electron microscope.

- *Chemical fixation* for biological specimens aims to stabilize the specimen's mobile macromolecular structure by chemical crosslinking of proteins with aldehydes such as formaldehyde and glutaraldehyde, and lipids with osmium tetroxide.
- *Cryofixation* – freezing a specimen so rapidly, to liquid nitrogen or even liquid helium temperatures, that the water forms vitreous (non-crystalline) ice. This preserves the specimen in a snapshot of its solution state. An entire field called cryo-electron microscopy has branched from this technique. With the development of cryo-electron microscopy of vitreous sections (CEMOVIS), it is now possible to observe samples from virtually any biological specimen close to its native state.
- *Dehydration* – freeze drying, or replacement of water with organic solvents such as ethanol or acetone, followed by critical point drying or infiltration with embedding resins.
- *Embedding, biological specimens* – after dehydration, tissue for observation in the transmission electron microscope is embedded so it can be sectioned ready for viewing. To do this the tissue is passed through a 'transition solvent' such as epoxy propane and then infiltrated with a resin such as Araldite epoxy resin; tissues may also be embedded directly in water-miscible acrylic resin. After the resin has been polymerised (hardened) the sample is thin sectioned (ultrathin sections) and stained - it is then ready for viewing.
- *Embedding, materials* - after embedding in resin, the specimen is usually ground and polished to a mirror-like finish using ultra-fine abrasives. The polishing process must be performed carefully to minimize scratches and other polishing artifacts that reduce image quality.
- *Sectioning* – produces thin slices of specimen, semitransparent to electrons. These can be cut on an ultramicrotome with a diamond knife to produce ultrathin slices about 60-90 nm thick. Disposable glass knives are also used because they can be made in the lab and are much cheaper.
- *Staining* – uses heavy metals such as lead, uranium or tungsten to scatter imaging electrons and thus give contrast between different structures, since many (especially biological) materials are nearly "transparent" to electrons (weak phase objects). In biology, specimens are can be stained "en bloc" before embedding and also later after sectioning. Typically thin sections are stained for several minutes with an aqueous or alcoholic solution of uranyl acetate followed by aqueous lead citrate.
- *Freeze-fracture or freeze-etch* – a preparation method particularly useful for examining lipid membranes and their incorporated proteins in "face on" view. The fresh tissue or cell suspension is frozen rapidly (cryofixed), then fractured by simply breaking or by using a microtome while maintained at liquid nitrogen temperature. The cold fractured surface (sometimes "etched" by increasing the temperature to about −100 °C for several minutes to let some ice sublime) is then shadowed with evaporated platinum or gold at an average angle of 45° in a high vacuum evaporator. A second coat of carbon, evaporated perpendicular to the average surface plane is often performed to improve stability of the replica coating. The specimen is returned to room temperature and pressure, then the extremely fragile "pre-shadowed" metal replica of the fracture surface is released from the underlying biological material by careful chemical digestion with acids, hypochlorite solution or SDS detergent. The still-floating replica is thoroughly washed from residual chemicals, carefully fished up on fine grids, dried then viewed in the TEM.

- *Ion Beam Milling* – thins samples until they are transparent to electrons by firing ions (typically argon) at the surface from an angle and sputtering material from the surface. A subclass of this is Focused ion beam milling, where gallium ions are used to produce an electron transparent membrane in a specific region of the sample, for example through a device within a microprocessor. Ion beam milling may also be used for cross-section polishing prior to SEM analysis of materials that are difficult to prepare using mechanical polishing.
- *Conductive Coating* – an ultrathin coating of electrically-conducting material, deposited either by high vacuum evaporation or by low vacuum sputter coating of the sample. This is done to prevent the accumulation of static electric fields at the specimen due to the electron irradiation required during imaging. Such coatings include gold, gold/palladium, platinum, tungsten, graphite etc. and are especially important for the study of specimens with the scanning electron microscope. Another reason for coating, even when there is more than enough conductivity, is to improve contrast, a situation more common with the operation of a FESEM (field emission SEM).

Disadvantages

Electron microscopes are expensive to build and maintain, but the capital and running costs of confocal light microscope systems now overlaps with those of basic electron microscopes. They are dynamic rather than static in their operation, requiring extremely stable high-voltage supplies, extremely stable currents to each electromagnetic coil/lens, continuously-pumped high- or ultra-high-vacuum systems, and a cooling water supply circulation through the lenses and pumps. As they are very sensitive to vibration and external magnetic fields, microscopes designed to achieve high resolutions must be housed in stable buildings (sometimes underground) with special services such as magnetic field cancelling systems. Some desktop low voltage electron microscopes have TEM capabilities at very low voltages (around 5 kV) without stringent voltage supply, lens coil current, cooling water or vibration isolation requirements and as such are much less expensive to buy and far easier to install and maintain, but do not have the same ultra-high (atomic scale) resolution capabilities as the larger instruments.



False-color SEM image of the filter setae of an Antarctic krill. (Raw electron microscope images carry no color information.)
Pictured: First degree filter setae with V-shaped second degree setae pointing towards the inside of the feeding basket. The purple ball is 1 µm in diameter.

The samples largely have to be viewed in vacuum, as the molecules that make up air would scatter the electrons. One exception is the environmental scanning electron microscope, which allows hydrated samples to be viewed in a low-pressure (up to 20 Torr/2.7 kPa), wet environment.

Scanning electron microscopes usually image conductive or semi-conductive materials best. Non-conductive materials can be imaged by an environmental scanning electron microscope. A common preparation technique is to coat the sample with a several-nanometer layer of conductive material, such as gold, from a sputtering machine; however, this process has the potential to disturb delicate samples.

Small, stable specimens such as carbon nanotubes, diatom frustules and small mineral crystals (asbestos fibres, for example) require no special treatment before being examined in the electron microscope. Samples of hydrated materials, including almost all biological specimens have to be prepared in various ways to stabilize them, reduce their thickness (ultrathin sectioning) and increase their electron optical contrast (staining). These processes may result in *artifacts*, but these can usually be identified by comparing the results obtained by using radically different specimen preparation methods. It is generally believed by scientists working in the field that as results from various preparation techniques have been compared and that there is no reason that they should all produce similar artifacts, it is reasonable to believe that electron microscopy features correspond with those of living cells. In addition,

higher-resolution work has been directly compared to results from X-ray crystallography, providing independent confirmation of the validity of this technique. Since the 1980s, analysis of cryofixed, vitrified specimens has also become increasingly used by scientists, further confirming the validity of this technique.[12] [13] [14]

Applications

Semiconductor and data storage

- Circuit edit
- Defect analysis
- Failure analysis

Biology and life sciences

- Diagnostic electron microscopy
- Cryobiology
- Protein localization
- Electron tomography
- Cellular tomography
- Cryo-electron microscopy
- Toxicology
- Biological production and viral load monitoring
- Particle analysis
- Pharmaceutical QC
- Structural biology
- 3D tissue imaging
- Virology
- Vitrification

Research

- Electron beam-induced deposition
- Materials qualification
- Materials and sample preparation
- Nanoprototyping
- Nanometrology
- Device testing and characterization

Industry

- High-resolution imaging
- 2D & 3D micro-characterization
- Macro sample to nanometer metrology
- Particle detection and characterization
- Direct beam-writing fabrication
- Dynamic materials experiments
- Sample preparation
- Forensics
- Mining (mineral liberation analysis)
- Chemical/Petrochemical

See also

- Category:Electron microscope images
- Field emission microscope
- HiRISE
- Scanning tunneling microscope
- Transmission Electron Aberration-corrected Microscope
- *Ultramicroscopy* (journal)

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External links

- Science Aid: Electron Microscopy (http://scienceaid.co.uk/biology/cell/analysingcells.html) High School (GCSE, A Level) resource
- Cell Centered Database - Electron microscopy data (http://ccdb.ucsd.edu/sand/main?typeid=4&event=showMPByType&start=1)

General

- Nanohedron.com|Nano image gallery (http://www.nanohedron.com/) beautiful images generated with electron microscopes.
- electron microscopy (http://www.microscopy.ethz.ch) Website of the ETH Zurich: Very good graphics and images, which illustrate various procedures.
- Environmental Scanning Electron Microscope (ESEM) (http://www.danilatos.com)
- X-ray element analysis in electron microscope (http://www.microanalyst.net/index_e.phtml) – Information portal with X-ray microanalysis and EDX contents

History

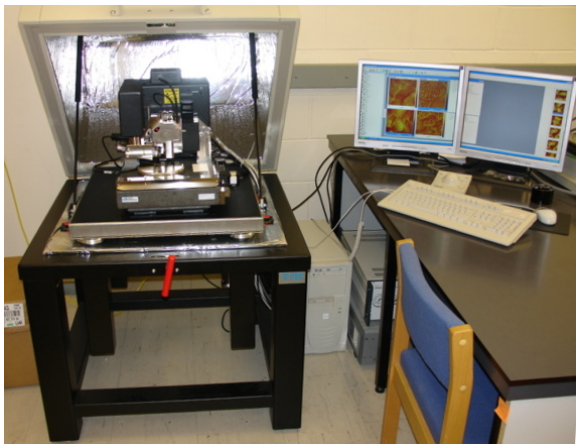
- John H.L. Watson: Very early Electron Microscopy in the Department of Physics, the University of Toronto – A personal recollection (http://www.physics.utoronto.ca/overview/history/microsco)
- Rubin Borasky Electron Microscopy Collection, 1930-1988 (http://americanhistory.si.edu/archives/d8452.htm) Archives Center, National Museum of American History, Smithsonian Institution.

Other

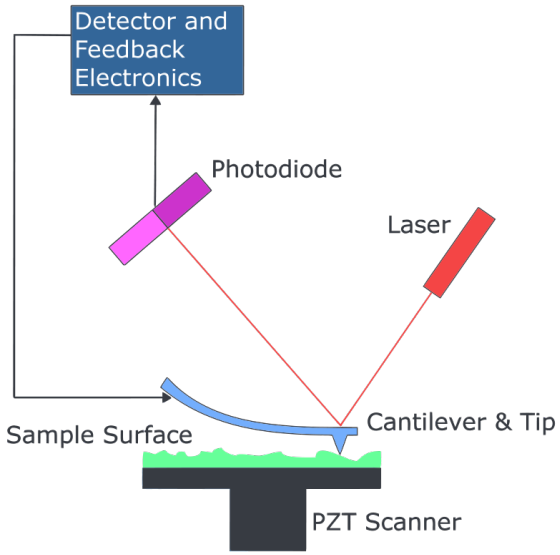
- The Royal Microscopical Society, Electron Microscopy Section (UK) (http://www.rms.org.uk/em.shtml)
- Albert Lleal micrograph. Scanning Electron Micrograph Coloured SEM (http://www.albertlleal.com/microphotography.html)

Atomic force microscope

Atomic force microscopy (AFM) or scanning force microscopy (SFM) is a very high-resolution type of scanning probe microscopy, with demonstrated resolution on the order of fractions of a nanometer, more than 1000 times better than the optical diffraction limit. The precursor to the AFM, the scanning tunneling microscope, was developed by Gerd Binnig and Heinrich Rohrer in the early 1980s at IBM Research - Zurich, a development that earned them the Nobel Prize for Physics in 1986. Binnig, Quate and Gerber invented the first atomic force microscope (also abbreviated as AFM) in 1986. The first commercially available atomic force microscope was introduced in 1989. The AFM is one of the foremost tools for imaging, measuring, and manipulating matter at the nanoscale. The information is gathered by "feeling" the surface with a mechanical probe. Piezoelectric elements that facilitate tiny but accurate and precise movements on (electronic) command enable the very precise scanning. In some variations, electric potentials can also be scanned using conducting cantilevers. In newer more advanced versions, currents can even be passed through the tip to probe the electrical conductivity or transport of the underlying surface, but this is much more challenging with very few groups reporting reliable data.

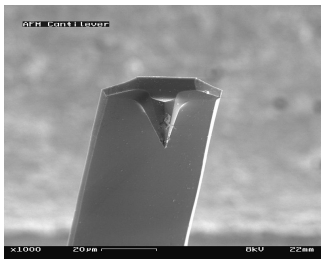


A commercial AFM setup

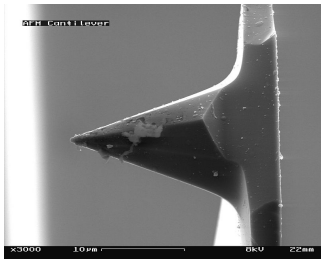


Block diagram of atomic force microscope

Basic principles



Electron micrograph of a used AFM cantilever image width ~100 micrometers...



and ~30 micrometers

The AFM consists of a cantilever with a sharp tip (probe) at its end that is used to scan the specimen surface. The cantilever is typically silicon or silicon nitride with a tip radius of curvature on the order of nanometers. When the tip is brought into proximity of a sample surface, forces between the tip and the sample lead to a deflection of the cantilever according to Hooke's law. Depending on the situation, forces that are measured in AFM include mechanical contact force, van der Waals forces, capillary forces, chemical bonding, electrostatic forces, magnetic forces (see magnetic force microscope, MFM), Casimir forces, solvation forces, etc. Along with force, additional quantities may simultaneously be measured through the use of specialized types of probe (see scanning thermal microscopy, photothermal microspectroscopy, etc.). Typically, the deflection is measured using a laser spot reflected from the top surface of the cantilever into an array of photodiodes. Other methods that are used include optical interferometry, capacitive sensing or piezoresistive AFM cantilevers. These cantilevers are fabricated with piezoresistive elements that act as a strain gauge. Using a Wheatstone bridge, strain in the AFM cantilever due to deflection can be measured, but this method is not as sensitive as laser deflection or interferometry.

If the tip was scanned at a constant height, a risk would exist that the tip collides with the surface, causing damage. Hence, in most cases a feedback mechanism is employed to adjust the tip-to-sample distance to maintain a constant force between the tip and the sample. Traditionally, the sample is mounted on a piezoelectric tube, that can move the sample in the z direction for maintaining a constant force, and the x and y directions for scanning the sample. Alternatively a 'tripod' configuration of three piezo crystals may be employed, with each responsible for scanning in the x,y and z directions. This eliminates some of the distortion effects seen with a tube scanner. In newer designs, the tip is mounted on a vertical piezo scanner while the sample is being scanned in X and Y using another piezo block. The resulting map of the area $s = f(x,y)$ represents the topography of the sample.

The AFM can be operated in a number of modes, depending on the application. In general, possible imaging modes are divided into static (also called *contact*) modes and a variety of dynamic (or non-contact) modes where the cantilever is vibrated.

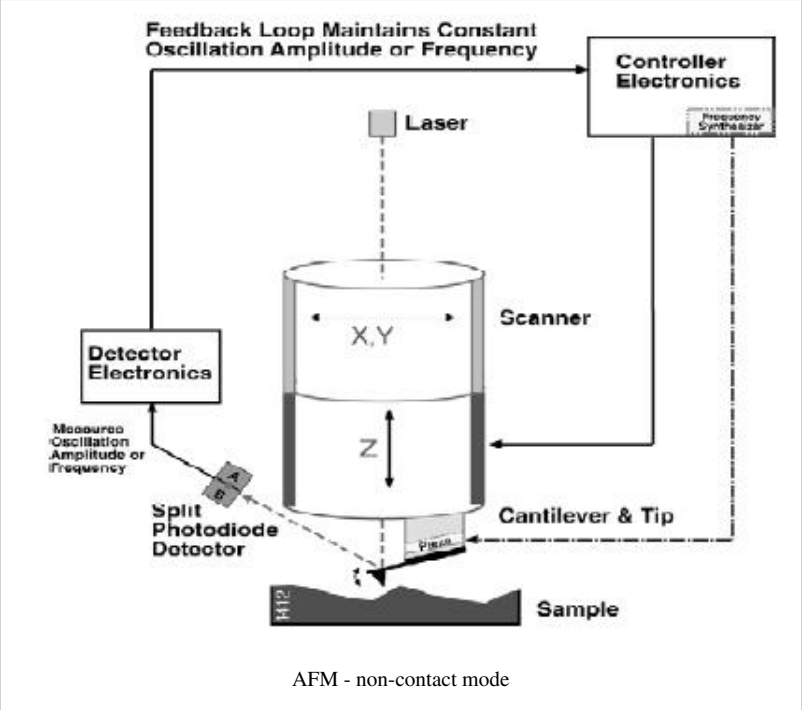
Imaging modes

The primary modes of operation for an AFM are static mode and dynamic mode. In static mode, the cantilever is "dragged" across the surface of the sample and the contours of the surface are measured directly using the deflection of the cantilever. In the dynamic mode, the cantilever is externally oscillated at or close to its fundamental resonance frequency or a harmonic. The oscillation amplitude, phase and resonance frequency are modified by tip-sample interaction forces. These changes in oscillation with respect to the external reference oscillation provide information about the sample's characteristics.

Contact mode

In the static mode operation, the static tip deflection is used as a feedback signal. Because the measurement of a static signal is prone to noise and drift, low stiffness cantilevers are used to boost the deflection signal. However, close to the surface of the sample, attractive forces can be quite strong, causing the tip to "snap-in" to the surface. Thus static mode AFM is almost always done in contact where the overall force is repulsive. Consequently, this technique is typically called "contact mode". In contact mode, the force between the tip and the surface is kept constant during scanning by maintaining a constant deflection.

Non-contact mode



AFM - non-contact mode

In this mode, the tip of the cantilever does not contact the sample surface. The cantilever is instead oscillated at a frequency slightly above its resonance frequency where the amplitude of oscillation is typically a few nanometers (<10 nm). The van der Waals forces, which are strongest from 1 nm to 10 nm above the surface, or any other long range force which extends above the surface acts to decrease the resonance frequency of the cantilever. This decrease in resonance frequency combined with the feedback loop system maintains a constant oscillation amplitude or frequency by adjusting the average tip-to-sample distance. Measuring the tip-to-sample distance at each (x,y) data point allows the scanning software to construct a topographic image of the sample surface.

Non-contact mode AFM does not suffer from tip or sample degradation effects that are sometimes observed after taking numerous scans with contact AFM. This makes non-contact AFM preferable to contact AFM for measuring soft samples. In the case of rigid samples, contact and non-contact images may look the same. However, if a few monolayers of adsorbed fluid are lying on the surface of a rigid sample, the images may look quite different. An AFM operating in contact mode will penetrate the liquid layer to image the underlying surface, whereas in non-contact mode an AFM will oscillate above the adsorbed fluid layer to image both the liquid and surface.

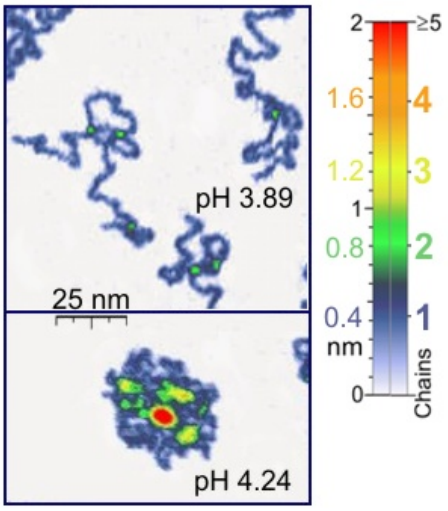
Schemes for dynamic mode operation include frequency modulation and the more common amplitude modulation. In frequency modulation, changes in the oscillation frequency provide information about tip-sample interactions. Frequency can be measured with very high sensitivity and thus the frequency modulation mode allows for the use of very stiff cantilevers. Stiff cantilevers provide stability very close to the surface and, as a result, this technique was the first AFM technique to provide true atomic resolution in ultra-high vacuum conditions.[1]

In amplitude modulation, changes in the oscillation amplitude or phase provide the feedback signal for imaging. In amplitude modulation, changes in the phase of oscillation can be used to discriminate between different types of materials on the surface. Amplitude modulation can be operated either in the non-contact or in the intermittent contact regime. In dynamic contact mode, the cantilever is oscillated such that the separation distance between the cantilever tip and the sample surface is modulated.

Amplitude modulation has also been used in the non-contact regime to image with atomic resolution by using very stiff cantilevers and small amplitudes in an ultra-high vacuum environment.

Tapping mode

In ambient conditions, most samples develop a liquid meniscus layer. Because of this, keeping the probe tip close enough to the sample for short-range forces to become detectable while preventing the tip from sticking to the surface presents a major problem for non-contact dynamic mode in ambient conditions. Dynamic contact mode (also called intermittent contact or tapping mode) was developed to bypass this problem.[3]



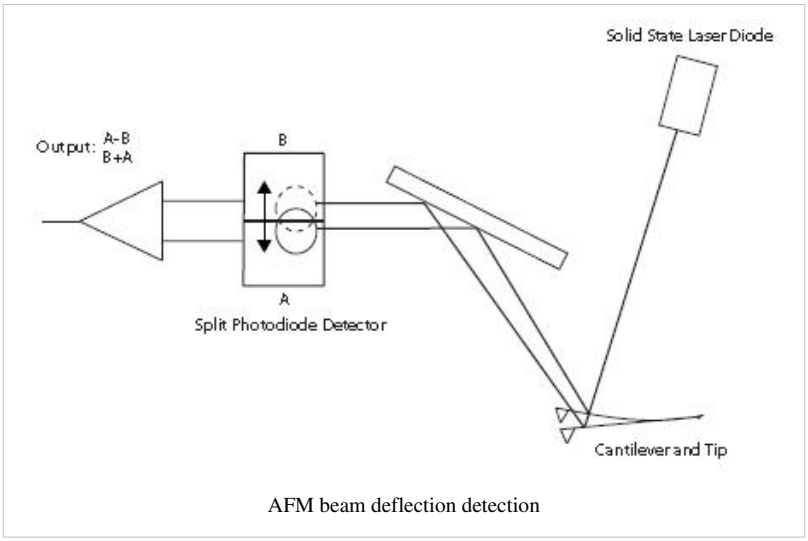
Single polymer chains (0.4 nm thick) recorded in a tapping mode under aqueous media with different pH.[2]

In *tapping mode*, the cantilever is driven to oscillate up and down at near its resonance frequency by a small piezoelectric element mounted in the AFM tip holder similar to non-contact mode. However, the amplitude of this oscillation is greater than 10 nm, typically 100 to 200 nm. Due to the interaction of forces acting on the cantilever when the tip comes close to the surface, Van der Waals force, dipole-dipole interaction, electrostatic forces, etc cause the amplitude of this oscillation to decrease as the tip gets closer to the sample. An electronic servo uses the piezoelectric actuator to control the height of the cantilever above the sample. The servo adjusts the height to maintain a set cantilever oscillation amplitude as the cantilever is scanned over the sample. A *tapping AFM* image is therefore produced by imaging the force of the intermittent contacts of the tip with the sample surface.

This method of "tapping" lessens the damage done to the surface and the tip compared to the amount done in contact mode. Tapping mode is gentle enough even for the visualization of supported lipid bilayers or adsorbed single polymer molecules (for instance, 0.4 nm thick chains of synthetic polyelectrolytes) under liquid medium. With proper scanning parameters, the conformation of single molecules can remain unchanged for hours.[2]

AFM cantilever deflection measurement

Laser light from a solid state diode is reflected off the back of the cantilever and collected by a position sensitive detector (PSD) consisting of two closely spaced photodiodes whose output signal is collected by a differential amplifier. Angular displacement of cantilever results in one photodiode collecting more light than the other photodiode, producing an output signal (the difference between the photodiode signals normalized by their sum) which is proportional to the deflection of the cantilever. It detects cantilever deflections <10 nm (thermal noise limited). A long beam path (several centimeters) amplifies changes in beam angle.



AFM beam deflection detection

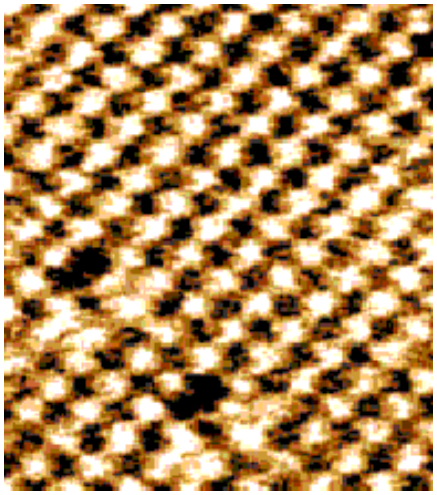
Force spectroscopy

Another major application of AFM (besides imaging) is force spectroscopy, the direct measurement of tip-sample interaction forces as a function of the gap between the tip and sample (the result of this measurement is called a force-distance curve). For this method, the AFM tip is extended towards and retracted from the surface as the deflection of the cantilever is monitored as a function of piezoelectric displacement. These measurements have been used to measure nanoscale contacts, atomic bonding, Van der Waals forces, and Casimir forces, dissolution forces in liquids and single molecule stretching and rupture forces.[4] Furthermore, AFM was used to measure in aqueous environment dispersion force due to polymer adsorbed on the substarte.[5] Forces of the order of a few piconewtons can now be routinely measured with a vertical distance resolution of better than 0.1 nanometer. Force spectroscopy can be performed with either static or dynamic modes. In dynamic modes, information about the cantilever vibration is monitored in addition to the static deflection.[6]

Problems with the technique include no direct measurement of the tip-sample separation and the common need for low stiffness cantilevers which tend to 'snap' to the surface. The snap-in can be reduced by measuring in liquids or by using stiffer cantilevers, but in the latter case a more sensitive deflection sensor is needed. By applying a small dither to the tip, the stiffness (force gradient) of the bond can be measured as well.[7]

Identification of individual surface atoms

The AFM can be used to image and manipulate atoms and structures on a variety of surfaces. The atom at the apex of the tip "senses" individual atoms on the underlying surface when it forms incipient chemical bonds with each atom. Because these chemical interactions subtly alter the tip's vibration frequency, they can be detected and mapped. This principle was used to distinguish between atoms of silicon, tin and lead on an alloy surface, by comparing these 'atomic fingerprints' to values obtained from large-scale density functional theory (DFT) simulations.[8]



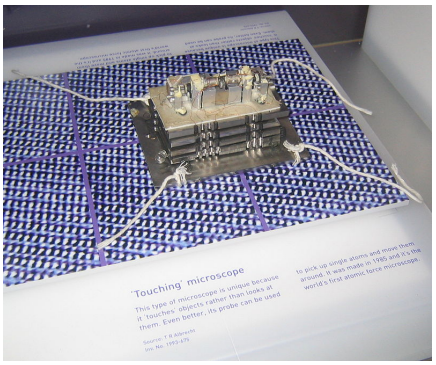
The atoms of a sodium chloride crystal viewed with an atomic force microscope

The trick is to first measure these forces precisely for each type of atom expected in the sample, and then to compare with forces given by DFT simulations. The team found that the tip interacted most strongly with silicon atoms, and interacted 23% and 41% less strongly with tin and lead atoms, respectively. Thus, each different type of atom can be identified in the matrix as the tip is moved across the surface.

Such a technique has been used now in biology and extended recently to cell biology. Forces corresponding to (i) the unbinding of receptor ligand couples (ii) unfolding of proteins (iii) cell adhesion at single cell scale have been gathered.

Advantages and disadvantages

Just like any other tool, an AFM's usefulness has limitations. When determining whether or not analyzing a sample with an AFM is appropriate, there are various advantages and disadvantages that must be considered.



The first atomic force microscope

Advantages

AFM has several advantages over the scanning electron microscope (SEM). Unlike the electron microscope which provides a two-dimensional projection or a two-dimensional image of a sample, the AFM provides a three-dimensional surface profile. Additionally, samples viewed by AFM do not require any special treatments (such as metal/carbon coatings) that would irreversibly change or damage the sample. While an electron microscope needs an expensive vacuum environment for proper operation, most AFM modes can work perfectly well in ambient air or even a liquid environment. This makes it possible to study biological macromolecules and even living organisms. In principle, AFM can provide higher resolution than SEM. It has been shown to give true atomic resolution in ultra-high vacuum (UHV) and, more recently, in liquid environments. High resolution AFM is comparable in resolution to scanning tunneling microscopy and transmission electron microscopy.

Disadvantages

A disadvantage of AFM compared with the scanning electron microscope (SEM) is the single scan image size. In one pass, the SEM can image an area on the order of square millimeters with a depth of field on the order of millimeters. Whereas the AFM can only image a maximum height on the order of 10-20 micrometers and a maximum scanning area of about 150×150 micrometers. One method of improving the scanned area size for AFM is by using parallel probes in a fashion similar to that of millipede data storage.

The scanning speed of an AFM is also a limitation. Traditionally, an AFM cannot scan images as fast as a SEM, requiring several minutes for a typical scan, while a SEM is capable of scanning at near real-time, although at relatively low quality. The relatively slow rate of scanning during AFM imaging often leads to thermal drift in the image[9] [10] making the AFM microscope less suited for measuring accurate distances between topographical features on the image. However, several fast-acting designs [11] [12] were suggested to increase microscope scanning productivity including what is being termed videoAFM (reasonable quality images are being obtained with videoAFM at video rate: faster than the average SEM). To eliminate image distortions induced by thermal drift, several methods have been introduced.[9] [10]

AFM images can also be affected by hysteresis of the piezoelectric material[13] and cross-talk between the *x*, *y*, *z* axes that may require software enhancement and filtering. Such filtering could "flatten" out real topographical features. However, newer AFMs utilize closed-loop scanners which practically eliminate these problems. Some AFMs also use separated orthogonal scanners (as opposed to a single tube) which also serve to eliminate part of the cross-talk problems.

As with any other imaging technique, there is the possibility of image artifacts, which could be induced by an unsuitable tip, a poor operating environment, or even by the sample itself. These image artifacts are unavoidable however, their occurrence and effect on results can be reduced through various methods.

Due to the nature of AFM probes, they cannot normally measure steep walls or overhangs. Specially made cantilevers and AFMs can be used to modulate the probe sideways as well as up and down (as with dynamic contact and non-contact modes) to measure sidewalls, at the cost of more expensive cantilevers, lower lateral resolution and additional artifacts.

Piezoelectric scanners

AFM scanners are made from piezoelectric material, which expands and contracts proportionally to an applied voltage. Whether they elongate or contract depends upon the polarity of the voltage applied. The scanner is constructed by combining independently operated piezo electrodes for X, Y, and Z into a single tube, forming a scanner which can manipulate samples and probes with extreme precision in 3 dimensions.

Scanners are characterized by their sensitivity which is the ratio of piezo movement to piezo voltage, i.e., by how much the piezo material extends or contracts per applied volt. Because of differences in material or size, the sensitivity varies from scanner to scanner. Sensitivity varies non-linearly with respect to scan size. Piezo scanners exhibit more sensitivity at the end than at the beginning of a scan. This causes the forward and reverse scans to behave differently and display hysteresis[13] between the two scan directions. This can be corrected by applying a non-linear voltage to the piezo electrodes to cause linear scanner movement and calibrating the scanner accordingly.[13]

The sensitivity of piezoelectric materials decreases exponentially with time. This causes most of the change in sensitivity to occur in the initial stages of the scanner's life. Piezoelectric scanners are run for approximately 48 hours before they are shipped from the factory so that they are past the point where they may have large changes in sensitivity. As the scanner ages, the sensitivity will change less with time and the scanner would seldom require recalibration.[14]

See also

- Frictional force mapping
- Scanning tunneling microscope
- Scanning probe microscopy
- Scanning voltage microscopy
- Surface force apparatus

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External links

- ME 597/PHYS 570: Fundamentals of Atomic Force Microscopy (http://nanohub.org/resources/7320)
- DoITPoMS Teaching and Learning Package - Atomic Force Microscopy (http://www.doitpoms.ac.uk/tlplib/afm/index.php)

Further reading

- SPM - Scanning Probe Microscopy Website (http://www.mobot.org/jwcross/spm/)
- Atomic Force Microscopy resource library (http://www.afmuniversity.org)
- R. W. Carpick and M. Salmeron, Scratching the surface: Fundamental investigations of tribology with atomic force microscopy (http://dx.doi.org/10.1021/cr960068q), Chemical Reviews, vol. 97, iss. 4, pp. 1163–1194 (2007).

Neutron scattering

Neutron scattering encompasses all scientific techniques whereby the deflection of neutron radiation is used as a scientific probe. Neutrons readily interact with atomic nuclei and magnetic fields from unpaired electrons, making a useful probe of both structure and magnetic order. Neutron Scattering falls into two basic categories - elastic and inelastic. Elastic scattering is when a neutron interacts with a nucleus or electronic magnetic field but does not leave it in an excited state, meaning the emitted neutron has the same energy as the injected neutron. Scattering processes that involve an energetic excitation or relaxation by the neutron are inelastic: the injected neutron's energy is used or increased to create an excitation or by absorbing the excess energy from a relaxation, and consequently the emitted neutron's energy is reduced or increased respectively.

For several good reasons, moderated neutrons provide an ideal tool for the study of almost all forms of condensed matter. Firstly, they are readily produced at a nuclear research reactor or a spallation source. Normally in such processes neutrons are however produced with much higher energies than are needed. Therefore moderators are generally used which slow the neutrons down and therefore produce wavelengths that are comparable to the atomic spacing in solids and liquids, and kinetic energies that are comparable to those of dynamic processes in materials. Moderators can be made from aluminium and filled with liquid hydrogen (for very long wavelength neutrons) or liquid methane (for shorter wavelength neutrons). Fluxes of 10^7/s - 10^8/s are not atypical in most neutron sources from any given moderator.

The neutrons cause pronounced interference and energy transfer effects in scattering experiments. Unlike an x-ray photon with a similar wavelength, which interacts with the electron cloud surrounding the nucleus, neutrons interact with the nucleus itself. Because the neutron is an electrically neutral particle, it is deeply penetrating, and is therefore more able to probe the bulk material. Consequently, it enables the use of a wide range of sample environments that

are difficult to use with synchrotron x-ray sources. It also has the advantage that the cross sections for interaction do not increase with atomic number as they do with radiation from a synchrotron x-ray source. Thus neutrons can be used to analyse materials with low atomic numbers like proteins and surfactants. This can be done at synchrotron sources but very high intensities are needed which may cause the structures to change. Moreover, the nucleus provides a very short range, isotropic potential varying randomly from isotope to isotope, making it possible to tune the nuclear scattering contrast to suit the experiment:

The neutron has an additional advantage over the x-ray photon in the study of condensed matter. It readily interacts with internal magnetic fields in the sample. In fact, the strength of the magnetic scattering signal is often very similar to that of the nuclear scattering signal in many materials, which allows the simultaneous exploration of both nuclear and magnetic structure. Because the neutron scattering amplitude can be measured in absolute units, both the structural and magnetic properties as measured by neutrons can be compared quantitatively with the results of other characterisation techniques.

See also

- Neutron diffraction
  - Small angle neutron scattering
  - Neutron Reflectometry
- Inelastic neutron scattering
  - neutron triple-axis spectrometry
  - neutron time-of-flight scattering
  - neutron backscattering
  - neutron spin echo
  - neutron resonance spin echo
- Neutron scattering facilities

Applications

Neutron scattering has been used to study various vibration modes, [1] including low-frequency collective motion in proteins and DNA, [2] [3] [4] [5] [6] as reviewed by Dr. P. Martel in 1992.[1]

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External links

- Neutron Scattering - A primer (http://knocknick.files.wordpress.com/2008/04/neutrons-a-primer-by-rogen-pynn.pdf) (LANL-hosted black and white version (http://library.lanl.gov/cgi-bin/getfile?00326651.pdf)) - An introductory article written by Roger Pynn (Los Alamos National Laboratory)
- Podcast Interview with two ILL scientists about neutron science/scattering at the ILL (http://omegataupodcast.net/2010/03/28-neutron-science-at-the-ill/)

ISIS neutron source

ISIS is a pulsed neutron and muon source. It is situated at the Rutherford Appleton Laboratory on the Harwell Science and Innovation Campus in Oxfordshire, United Kingdom and is part of the Science and Technology Facilities Council . It uses the techniques muon spectroscopy and neutron scattering to probe the structure and dynamics of condensed matter on a microscopic scale ranging from the subatomic to the macromolecular.

ISIS Logo

ISIS experimental hall for Target Station 1

Hundreds of experiments are performed annually at ISIS by visiting researchers from around the world, in diverse science areas including physics, chemistry, materials engineering, earth sciences, biology and archaeology.

Neutrons and muons

Neutrons are uncharged constituents of atoms and penetrate materials well, deflecting only from the nuclei of atoms. The statistical accumulation of deflected neutrons at different positions beyond the sample can be used to find the structure of a material, and the loss or gain of energy by neutrons can reveal the dynamic behaviour of parts of a sample, for example diffusive processes in solids. At ISIS the neutrons are created by accelerating 'bunches' of protons in a synchrotron, then colliding these with a heavy tantalum metal target, under a constant cooling load to dissipate the heat from the 160 kW proton beam. The impacts cause neutrons to spall off the tantalum atoms, and the neutrons are channelled through guides, or beamlines, to about 20 instruments, individually optimised for the study of different types of matter. The target station and most of the instruments are set in a large hall. Neutrons are a dangerous form of radiation, so the target and beamlines are heavily shielded with concrete.

ISIS produces muons by colliding a fraction of the proton beam with a graphite target, producing pions which decay rapidly into muons, delivered in a spin-polarised beam to sample stations.

Science at ISIS

Another view of the ISIS experimental hall for Target Station 1

ISIS is administered and operated by the Science and Technology Facilities Council (previously CCLRC). Experimental time is open to academic users from funding countries and is applied for through a twice-yearly 'call for proposals'. Research allocation, or 'beam-time', is allotted to applicants via a peer-review process. Users and their parent institutions do not pay for the running costs of the facility, which are as much as £11,000 per instrument per day. Their transport and living costs are also refunded whilst carrying out the experiment. Most users stay in Ridgeway House, a hotel near the site, or at Cosener's House, an STFC-run conference centre in Abingdon. Over 600 experiments by 1600 users are completed every year.

A large number of support staff operate the facility, aid users, and carry out research, the control room is staffed 24 hours a day, every day of the year. Instrument scientists oversee the running of each instrument and liaise with users, and other divisions provide sample environment, data analysis and computing expertise, maintain the accelerator, and run education programmes.

Among the important and pioneering work carried out was the discovery of the structure of high-temperature superconductors and the solid phase of buckminster-fullerene.

Construction for a second target station started in 2003, and the first neutrons were delivered to the target on December 14, 2007[1] . It will use low-energy neutrons to study soft condensed matter, biological systems, advanced composites and nanomaterials. To supply the extra protons for this, the accelerator is being upgraded.

History and background of ISIS

The source was approved in 1977 for the RAL site on the Harwell campus and recycled components from earlier UK science programmes including the accelerator hall which had previously been occupied by the Nimrod accelerator. The first beam was produced in 1984, and the facility was formally opened by the then Prime Minister Margaret Thatcher in October 1985.[2]

The name ISIS is not an acronym: it refers to the Ancient Egyptian goddess and the local name for the River Thames. The name was selected for the official opening of the facility in 1985, prior to this it was known as the SNS, or Spallation Neutron Source. The name was considered appropriate as Isis was a goddess who could restore life to the dead, and ISIS made use of equipment previously constructed for the Nimrod and Nina accelerators[3] .

External links

- ISIS facility [4]
- ISIS Second Target Station [5]
- The Science and Technology Facilities Council [6]

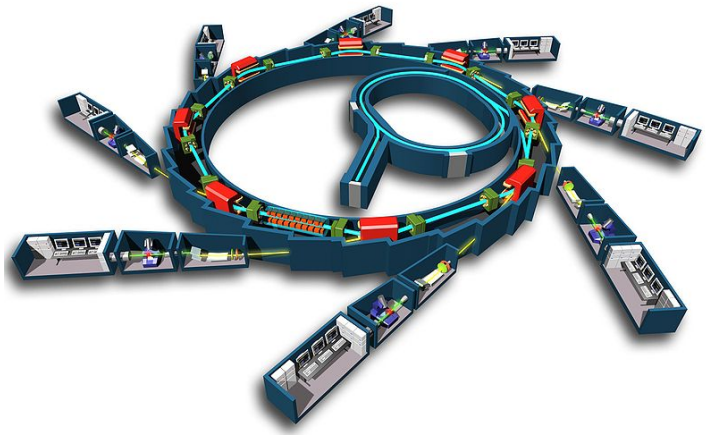
References

[1] ISIS Second Target Station Project (http://ts-2.isis.rl.ac.uk/)
[2] Linacs at the Rutherford Appleton Laboratory (http://epubs.cclrc.ac.uk/bitstream/692/linacplahistory.pdf)
[3] Explanation of the name of ISIS (http://www.isis.rl.ac.uk/aboutIsis/index.htm)
[4] http://www.isis.stfc.ac.uk/
[5] http://www.isis.stfc.ac.uk/about-isis/target-station-2/
[6] http://www.stfc.ac.uk

Geographical coordinates: 51°34′18″N 1°19′12″W

Synchrotron

A **synchrotron** is a particular type of cyclic particle accelerator in which the magnetic field (to turn the particles so they circulate) and the electric field (to accelerate the particles) are carefully synchronised with the travelling particle beam. The proton synchrotron was originally conceived by Sir Marcus Oliphant[1] . The honour of being the first to publish the idea went to Vladimir Veksler, and the first electron synchrotron was constructed by Edwin McMillan.



Here, the synchrotron is the circular track, off which the beamlines branch.

Characteristics

While a cyclotron uses a constant magnetic field and a constant-frequency applied electric field (one of these is varied in the synchrocyclotron), both of these fields are varied in the synchrotron. By increasing these parameters appropriately as the particles gain energy, their path can be held constant as they are accelerated. This allows the vacuum chamber for the particles to be a large thin torus. In reality it is easier to use some straight sections between the bending magnets and some bent sections within the magnets giving the torus the shape of a round-cornered polygon. A path of large effective radius may thus be constructed using simple straight and curved pipe segments, unlike the disc-shaped chamber of the cyclotron type devices. The shape also allows and requires the use of multiple magnets to bend the particle beams. Straight sections are required at spacings around a ring for both radiofrequency cavities, and in third generation setups space is allowed for insertion of energy extraction devices such as wigglers and undulators.

The maximum energy that a cyclic accelerator can impart is typically limited by the strength of the magnetic field(s) and the minimum radius (maximum curvature) of the particle path.

The interior of the Australian Synchrotron facility. Dominating the image is the storage ring, showing the optical diagnostic beamline at front right. In the middle of the storage ring is the booster synchrotron and linac

In a cyclotron the maximum radius is quite limited as the particles start at the center and spiral outward, thus the entire path must be a self-supporting disc-shaped evacuated chamber. Since the radius is limited, the power of the machine becomes limited by the strength of the magnetic field. In the case of an ordinary electromagnet the field strength is limited by the saturation of the core (when all magnetic domains are aligned the field may not be further increased to any practical extent). The arrangement of the single pair of magnets the full width of the device also limits the economic size of the device.

Synchrotrons overcome these limitations, using a narrow beam pipe which can be surrounded by much smaller and more tightly focusing magnets. The ability of this device to accelerate particles is limited by the fact that the particles must be charged to be accelerated at all, but charged particles under acceleration emit photons (light), thereby losing energy. The limiting beam energy is reached when the energy lost to the lateral acceleration required to maintain the beam path in a circle equals the energy added each cycle. More powerful accelerators are built by using large radius paths and by using more numerous and more powerful microwave cavities to accelerate the particle beam between corners. Lighter particles (such as electrons) lose a larger fraction of their energy when turning. Practically speaking, the energy of electron/positron accelerators is limited by this radiation loss, while it does not play a significant role in the dynamics of proton or ion accelerators. The energy of those is limited strictly by the strength of magnets and by the cost.

Design and operation

Particles are injected into the main ring at substantial energies by either a linear accelerator or by an intermediate synchrotron which is in turn fed by a linear accelerator. The "linac" is in turn fed by particles accelerated to intermediate energy by a simple high voltage power supply, typically a Cockcroft-Walton generator.

Starting from an appropriate initial value determined by the injection velocity the magnetic field is then increased. The particles pass through an electrostatic accelerator driven by a high alternating voltage. At particle speeds not close to the speed of light the frequency of the accelerating voltage can be made roughly proportional to the current in the bending magnets. A finer control of the frequency is performed by a servo loop which responds to the detection of the passing of the traveling group of particles. At particle speeds approaching light speed the frequency becomes more nearly constant, while the current in the bending magnets continues to increase. The maximum energy that can be applied to the particles (for a given ring size and magnet count) is determined by the saturation of the cores of the bending magnets (the point at which increasing current does not produce additional magnetic field). One way to obtain additional power is to make the torus larger and add additional bending magnets. This allows the amount of particle redirection at saturation to be less and so the particles can be more energetic. Another means of obtaining higher power is to use superconducting magnets, these not being limited by core saturation.

Large synchrotrons

One of the early large synchrotrons, now retired, is the Bevatron, constructed in 1950 at the Lawrence Berkeley Laboratory. The name of this proton accelerator comes from its power, in the range of 6.3 GeV (then called BeV for billion electron volts; the name predates the adoption of the SI prefix giga-). A number of heavy elements, unseen in the natural world, were first created with this machine. This site is also the location of one of the first large bubble chambers used to examine the results of the atomic collisions produced here.

Modern industrial-scale synchrotrons can be very large (here, Soleil near Paris)

Another early large synchrotron is the Cosmotron built at Brookhaven National Laboratory which reached 3.3 GeV in 1953.[2]

Until August 2008, the highest energy synchrotron in the world was the Tevatron, at the Fermi National Accelerator Laboratory, in the United States. It accelerates protons and antiprotons to slightly less than 1 TeV of kinetic energy and collides them together. The Large Hadron Collider (LHC), which has been built at the European Laboratory for High Energy Physics (CERN), has roughly seven times this energy (so proton-proton collisions occur at roughly 14 TeV). It is housed in the 27 km tunnel which formerly housed the Large Electron Positron (LEP) collider, so it will maintain the claim as the largest scientific device ever built. The LHC will also accelerate heavy ions (such as lead) up to an energy of 1.15 PeV.

The largest device of this type seriously proposed was the Superconducting Super Collider (SSC), which was to be built in the United States. This design, like others, used superconducting magnets which allow more intense magnetic fields to be created without the limitations of core saturation. While construction was begun, the project was cancelled in 1994, citing excessive budget overruns — this was due to naïve cost estimation and economic management issues rather than any basic engineering flaws. It can also be argued that the end of the Cold War resulted in a change of scientific funding priorities that contributed to its ultimate cancellation. While there is still potential for yet more powerful proton and heavy particle cyclic accelerators, it appears that the next step up in electron beam energy must avoid losses due to synchrotron radiation. This will require a return to the linear accelerator, but with devices significantly longer than those currently in use. There is at present a major effort to design and build the International Linear Collider (ILC), which will consist of two opposing linear accelerators, one for electrons and one for positrons. These will collide at a total center of mass energy of 0.5 TeV.

However, synchrotron radiation also has a wide range of applications (see synchrotron light) and many 2nd and 3rd generation synchrotrons have been built especially to harness it. The largest of those 3rd generation synchrotron light sources are the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, the Advanced Photon Source (APS) near Chicago, USA, and SPring-8 in Japan, accelerating electrons up to 6, 7 and 8 GeV, respectively.

Synchrotrons which are useful for cutting edge research are large machines, costing tens or hundreds of millions of dollars to construct, and each beamline (there may be 20 to 50 at a large synchrotron) costs another two or three million dollars on average. These installations are mostly built by the science funding agencies of governments of developed countries, or by collaborations between several countries in a region, and operated as infrastructure facilities available to scientists from universities and research organisations throughout the country, region, or world. More compact models, however, have been developed, such as the Compact Light Source.

List of installations

Synchrotron	Location & Country	Energy (GeV)	Circumference (m)	Commissioned	Decommissioned
Advanced Photon Source (APS)	Argonne National Laboratory, USA	7.0	1104	1995	
ALBA	Cerdanyola del Vallès near Barcelona, Spain	3	270	2010	
ISIS	Rutherford Appleton Laboratory, UK	0.8	163	1985	
Australian Synchrotron	Melbourne, Australia	3	216	2006	
ANKA	Karlsruhe Institute of Technology, Germany	2.5	110.4	2000	
LNLS	Campinas, Brazil	1.37	93.2	1997	
SESAME	Allaan, Jordan	2.5	125	Under Design	
Bevatron	Lawrence Berkeley Laboratory, USA	6	114	1954	1993
Advanced Light Source	Lawrence Berkeley Laboratory, USA	1.9	196.8	1993	
Cosmotron	Brookhaven National Laboratory, USA	3	72	1953	1968
National Synchrotron Light Source	Brookhaven National Laboratory, USA	2.8	170	1982	
Nimrod	Rutherford Appleton Laboratory, UK	7		1957	1978
Alternating Gradient Synchrotron (AGS)	Brookhaven National Laboratory, USA	33	800	1960	
Stanford Synchrotron Radiation Lightsource	SLAC National Accelerator Laboratory, USA	3	234	1973	
Synchrotron Radiation Center (SRC)	Madison, USA	1	121	1968	
Cornell High Energy Synchrotron Source (CHESS)	Cornell University, USA	5.5	768	1979	
Soleil	Paris, France	3	354	2006	
Shanghai Synchrotron Radiation Facility (SSRF)	Shanghai, China	3.5	432	2007	
Proton Synchrotron	CERN, Switzerland	28	628.3	1959	
Tevatron	Fermi National Accelerator Laboratory, USA	1000	6300	1983	
Swiss Light Source	Paul Scherrer Institute, Switzerland	2.8	288	2001	
Large Hadron Collider (LHC)	CERN, Switzerland	7000	26659	2008	
BESSY II	Helmholtz-Zentrum Berlin in Berlin, Germany	1.7	240	1998	
European Synchrotron Radiation Facility (ESRF)	Grenoble, France	6	844	1992	
MAX-I	MAX-lab, Sweden	0.55	30	1986	
MAX-II	MAX-lab, Sweden	1.5	90	1997	
MAX-III	MAX-lab, Sweden	0.7	36	2008	
ELETTRA	Trieste, Italy	2-2.4	260	1993	
Synchrotron Radiation Source	Daresbury Laboratory, UK	2	96	1980	2008

ASTRID	Aarhus University, Denmark	0.58	40	1991	
Diamond Light Source	Oxfordshire, UK	3	561.6	2006	
DORIS III	DESY, Germany	4.5	289	1980	
PETRA II	DESY, Germany	12	2304	1995	2007
PETRA III	DESY, Germany	6.5	2304	2009	
Canadian Light Source	University of Saskatchewan, Canada	2.9	171	2002	
SPring-8	RIKEN, Japan	8	1436	1997	
KEK	Tsukuba, Japan	12			
National Synchrotron Radiation Research Center	Hsinchu Science Park, Taiwan	3.3	518.4	2008	
Synchrotron Light Research Institute (SLRI)	Nakhon Ratchasima, Thailand	1.2	81.4	2004	
Indus 1	Raja Ramanna Centre for Advanced Technology, Indore, India	0.45		1999	
Indus 2	Raja Ramanna Centre for Advanced Technology, Indore, India	2.5	36	2005	
Synchrophasotron	JINR, Dubna, Russia	10	180	1957	2005
U-70 synchrotron	IHEP, Protvino, Russia	70		1967	
CAMD	LSU, Louisiana, US	1.5	-	-	
PLS	PAL, Pohang, Korea	2.5	280.56	1994	

- Note: in the case of colliders, the quoted energy is often double what is shown here. The above table shows the energy of one beam but if two opposing beams collide head on, the centre of mass energy is double the beam energy shown.

Applications

- Life sciences: protein and large molecule crystallography
- LIGA based microfabrication
- Drug discovery and research
- "Burning" computer chip designs into metal wafers
- Studying molecule shapes and protein crystals
- Analysing chemicals to determine their composition
- Observing the reaction of living cells to drugs
- Inorganic material crystallography and microanalysis
- Fluorescence studies
- Semiconductor material analysis and structural studies
- Geological material analysis
- Medical imaging
- Proton therapy to treat some forms of cancer

See also

- List of synchrotron radiation facilities
- Synchrotron X-ray tomographic microscopy
- Energy amplifier
- Superconducting Radio Frequency

References

[1] Nature 407, 468 (28 September 2000) (http://www.nature.com/nature/journal/v407/n6803/full/407468a0.html).
[2] The Cosmotron (http://www.bnl.gov/bnlweb/history/cosmotron.asp)

External links

- Canadian Light Source (http://www.lightsource.ca)
- Australian Synchrotron (http://www.synchrotron.org.au)
- Diamond UK Synchrotron (http://www.diamond.ac.uk)
- Lightsources.org (http://www.lightsources.org/cms/)
- CERN Large Hadron Collider (http://lhc-new-homepage.web.cern.ch/lhc-new-homepage)
- Synchrotron Light Sources of the World (http://www-als.lbl.gov/als/synchrotron_sources.html)
- A Miniature Synchrotron: (http://www.technologyreview.com/Biotech/20149/) room-size synchrotron offers scientists a new way to perform high-quality x-ray experiments in their own labs, *Technology Review*, February 04, 2008
- Brazilian Synchrotron Light Laboratory (http://www.lnls.br/lnls/cgi/cgilua.exe/sys/start.htm?UserActiveTemplate=lnls_2007_english&tpl=home)
- Podcast interview (http://omegataupodcast.net/2009/03/28/11-synchrotron-radiation-science-at-esrf/) with a scientist at the European Synchrotron Radiation Facility

Complex Systems Biology and Biostatistics

Biochemistry

Biochemistry is the study of chemical processes in living organisms. Biochemistry governs all living organisms and living processes. By controlling information flow through biochemical signalling and the flow of chemical energy through metabolism; biochemical processes give rise to the seemingly magical phenomenon of life. Much of biochemistry deals with the structures and functions of cellular components such as proteins, carbohydrates, lipids, nucleic acids and other biomolecules although increasingly processes rather than individual molecules are the main focus. Over the last 40 years biochemistry has become so successful at explaining living processes that now almost all areas of the life sciences from botany to medicine are engaged in biochemical research. Today the main focus of pure biochemistry is in understanding how biological molecules give rise to the processes that occur within living cells which in turn relates greatly to the study and understanding of whole organisms.

Among the vast number of different biomolecules, many are complex and large molecules (called *polymers*), which are composed of similar repeating subunits (called *monomers*). Each class of polymeric biomolecule has a different set of subunit types.[1] For example, a protein is a polymer whose subunits are selected from a set of 20 or more amino acids. Biochemistry studies the chemical properties of important biological molecules, like proteins, and in particular the chemistry of enzyme-catalyzed reactions.

The biochemistry of cell metabolism and the endocrine system has been extensively described. Other areas of biochemistry include the genetic code (DNA, RNA), protein synthesis, cell membrane transport, and signal transduction.

History

Originally, it was generally believed that life was not subject to the laws of science the way non-life was. It was thought that only living beings could produce the molecules of life (from other, previously existing biomolecules). Then, in 1828, Friedrich Wöhler published a paper on the synthesis of urea, proving that organic compounds can be created artificially.[2] [3]

The dawn of biochemistry may have been the discovery of the first enzyme, diastase (today called amylase), in 1833 by Anselme Payen. Eduard Buchner contributed the first demonstration of a complex biochemical process outside of a cell in 1896: alcoholic fermentation in cell extracts of yeast. Although the term “biochemistry” seems to have been first used in 1882, it is generally accepted that the formal coinage of biochemistry occurred in 1903 by Carl Neuberg, a German chemist. Previously, this area would have been referred to as physiological chemistry. Since then, biochemistry has advanced, especially since the mid-20th century, with the development of new techniques such as chromatography, X-ray diffraction, dual polarisation interferometry, NMR spectroscopy, radioisotopic labeling, electron microscopy and molecular dynamics simulations. These techniques allowed for the discovery and detailed analysis of many molecules and metabolic pathways of the cell, such as glycolysis and the Krebs cycle (citric acid cycle).

Another significant historic event in biochemistry is the discovery of the gene and its role in the transfer of information in the cell. This part of biochemistry is often called molecular biology. In the 1950s, James D. Watson, Francis Crick, Rosalind Franklin, and Maurice Wilkins were instrumental in solving DNA structure and suggesting its relationship with genetic transfer of information. In 1958, George Beadle and Edward Tatum received the Nobel Prize for work in fungi showing that one gene produces one enzyme. In 1988, Colin Pitchfork was the first person convicted of murder with DNA evidence, which led to growth of forensic science. More recently, Andrew Z. Fire

and Craig C. Mello received the 2006 Nobel Prize for discovering the role of RNA interference (RNAi), in the silencing of gene expression

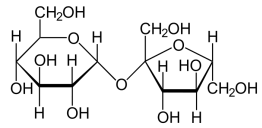
Today, there are three main types of biochemistry. Plant biochemistry involves the study of the biochemistry of autotrophic organisms such as photosynthesis and other plant specific biochemical processes. General biochemistry encompasses both plant and animal biochemistry. Human/medical/medicinal biochemistry focuses on the biochemistry of humans and medical illnesses.

Monomers and polymers

The four main classes of molecules in biochemistry are carbohydrates, lipids, proteins, and nucleic acids. Many biological molecules are polymers: in this terminology, ***monomers*** are relatively small micromolecules that are linked together to create large macromolecules, which are known as ***polymers***. When monomers are linked together to synthesize a biological polymer, they undergo a process called dehydration synthesis.

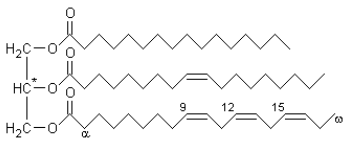
Carbohydrates

Carbohydrates are made from monomers called *monosaccharides*. Some of these monosaccharides include glucose ($C_6H_{12}O_6$), fructose ($C_6H_{12}O_6$), and deoxyribose ($C_5H_{10}O_4$). When two monosaccharides undergo dehydration synthesis, water is produced, as two hydrogen atoms and one oxygen atom are lost from the two monosaccharides' hydroxyl group.



A molecule of sucrose (glucose + fructose), a disaccharide.

Lipids



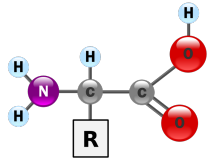
A triglyceride with a glycerol molecule on the left and three fatty acids coming off it.

Lipids are usually made from one molecule of glycerol combined with other molecules. In triglycerides, the main group of bulk lipids, there is one molecule of glycerol and three fatty acids. Fatty acids are considered the monomer in that case, and may be saturated (no double bonds in the carbon chain) or unsaturated (one or more double bonds in the carbon chain).

Lipids, especially phospholipids, are also used in various pharmaceutical products, either as co-solubilisers (e.g. in parenteral infusions) or else as drug carrier components (e.g. in a liposome or transfersome).

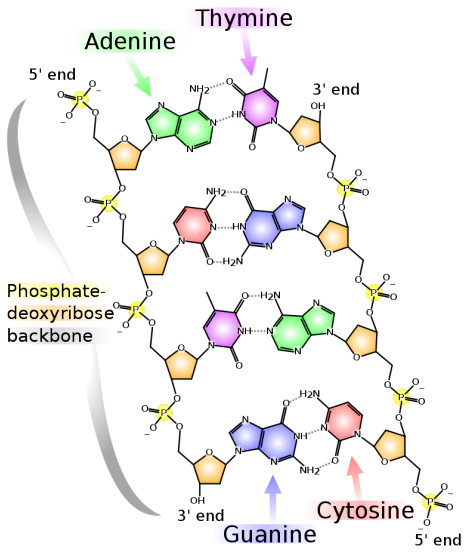
Proteins

Proteins are very large molecules – macro-biopolymers – made from monomers called *amino acids*. There are 20 standard amino acids, each containing a carboxyl group, an amino group, and a side chain (known as an "R" group). The "R" group is what makes each amino acid different, and the properties of the side chains greatly influence the overall three-dimensional conformation of a protein. When amino acids combine, they form a special bond called a peptide bond through dehydration synthesis, and become a ***polypeptide***, or protein.



The general structure of an α-amino acid, with the amino group on the left and the carboxyl group on the right.

Nucleic acids



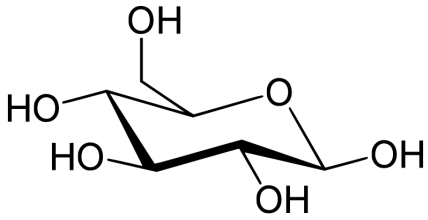
The structure of deoxyribonucleic acid (DNA), the picture shows the monomers being put together.

Nucleic acids are the molecules that make up DNA, an extremely important substance which all cellular organisms use to store their genetic information. The most common nucleic acids are deoxyribonucleic acid and ribonucleic acid. Their monomers are called nucleotides. The most common nucleotides are adenine, cytosine, guanine, thymine, and uracil. Adenine binds with thymine and uracil; thymine only binds with adenine; and cytosine and guanine can only bind with each other.

Carbohydrates

The function of carbohydrates includes energy storage and providing structure. Sugars are carbohydrates, but not all carbohydrates are sugars. There are more carbohydrates on Earth than any other known type of biomolecule; they are used to store energy and genetic information, as well as play important roles in cell to cell interactions and communications.

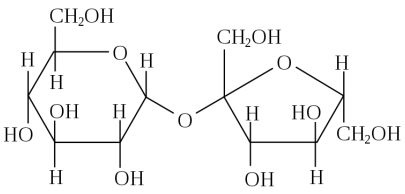
Monosaccharides



Glucose

The simplest type of carbohydrate is a monosaccharide, which among other properties contains carbon, hydrogen, and oxygen, mostly in a ratio of 1:2:1 (generalized formula $C_nH_{2n}O_n$, where n is at least 3). Glucose, one of the most important carbohydrates, is an example of a monosaccharide. So is fructose, the sugar commonly associated with the sweet taste of fruits.[4] [a] Some carbohydrates (especially after condensation to oligo- and polysaccharides) contain less carbon relative to H and O, which still are present in 2:1 (H:O) ratio. Monosaccharides can be grouped into aldoses (having an aldehyde group at the end of the chain, e. g. glucose) and ketoses (having a keto group in their chain; e. g. fructose). Both aldoses and ketoses occur in an equilibrium (starting with chain lengths of C4) cyclic forms. These are generated by bond formation between one of the hydroxyl groups of the sugar chain with the carbon of the aldehyde or keto group to form a hemiacetal bond. This leads to saturated five-membered (in furanoses) or six-membered (in pyranoses) heterocyclic rings containing one O as heteroatom.

Disaccharides



Sucrose: ordinary table sugar and probably the most familiar carbohydrate.

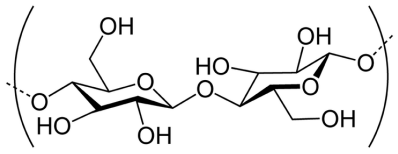
Two monosaccharides can be joined together using dehydration synthesis, in which a hydrogen atom is removed from the end of one molecule and a hydroxyl group (—OH) is removed from the other; the remaining residues are then attached at the sites from which the atoms were removed. The H—OH or H_2O is then released as a molecule of water, hence the term *dehydration*. The new molecule, consisting of two monosaccharides, is called a *disaccharide* and is conjoined together by a glycosidic or ether bond. The reverse reaction can also

occur, using a molecule of water to split up a disaccharide and break the glycosidic bond; this is termed *hydrolysis*. The most well-known disaccharide is sucrose, ordinary sugar (in scientific contexts, called *table sugar* or *cane sugar* to differentiate it from other sugars). Sucrose consists of a glucose molecule and a fructose molecule joined together. Another important disaccharide is lactose, consisting of a glucose molecule and a galactose molecule. As most humans age, the production of lactase, the enzyme that hydrolyzes lactose back into glucose and galactose, typically decreases. This results in lactase deficiency, also called *lactose intolerance*.

Sugar polymers are characterised by having reducing or non-reducing ends. A reducing end of a carbohydrate is a carbon atom which can be in equilibrium with the open-chain aldehyde or keto form. If the joining of monomers takes place at such a carbon atom, the free hydroxy group of the pyranose or furanose form is exchanged with an OH-side chain of another sugar, yielding a full acetal. This prevents opening of the chain to the aldehyde or keto form and renders the modified residue non-reducing. Lactose contains a reducing end at its glucose moiety, whereas the galactose moiety form a full acetal with the C4-OH group of glucose. Saccharose does not have a reducing end because of full acetal formation between the aldehyde carbon of glucose (C1) and the keto carbon of fructose (C2).

Oligosaccharides and polysaccharides

When a few (around three to six) monosaccharides are joined together, it is called an *oligosaccharide* (*oligo-* meaning "few"). These molecules tend to be used as markers and signals, as well as having some other uses. Many monosaccharides joined together make a polysaccharide. They can be joined together in one long linear chain, or they may be branched. Two of the most common polysaccharides are cellulose and glycogen, both consisting of repeating glucose monomers.



Cellulose as polymer of β-D-glucose

- *Cellulose* is made by plants and is an important structural component of their cell walls. Humans can neither manufacture nor digest it.
- *Glycogen*, on the other hand, is an animal carbohydrate; humans and other animals use it as a form of energy storage.

Use of carbohydrates as an energy source

Glucose is the major energy source in most life forms. For instance, polysaccharides are broken down into their monomers (glycogen phosphorylase removes glucose residues from glycogen). Disaccharides like lactose or sucrose are cleaved into their two component monosaccharides.

Glycolysis (anaerobic)

Glucose is mainly metabolized by a very important ten-step pathway called glycolysis, the net result of which is to break down one molecule of glucose into two molecules of pyruvate; this also produces a net two molecules of ATP, the energy currency of cells, along with two reducing equivalents in the form of converting NAD^+ to NADH. This does not require oxygen; if no oxygen is available (or the cell cannot use oxygen), the NAD is restored by converting the pyruvate to lactate (lactic acid) (e. g. in humans) or to ethanol plus carbon dioxide (e. g. in yeast). Other monosaccharides like galactose and fructose can be converted into intermediates of the glycolytic pathway.

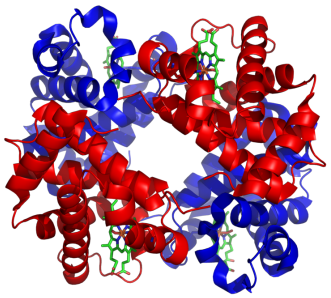
Aerobic

In aerobic cells with sufficient oxygen, like most human cells, the pyruvate is further metabolized. It is irreversibly converted to acetyl-CoA, giving off one carbon atom as the waste product carbon dioxide, generating another reducing equivalent as NADH. The two molecules acetyl-CoA (from one molecule of glucose) then enter the citric acid cycle, producing two more molecules of ATP, six more NADH molecules and two reduced (ubi)quinones (via $FADH_2$ as enzyme-bound cofactor), and releasing the remaining carbon atoms as carbon dioxide. The produced NADH and quinol molecules then feed into the enzyme complexes of the respiratory chain, an electron transport system transferring the electrons ultimately to oxygen and conserving the released energy in the form of a proton gradient over a membrane (inner mitochondrial membrane in eukaryotes). Thereby, oxygen is reduced to water and the original electron acceptors NAD^+ and quinone are regenerated. This is why humans breathe in oxygen and breathe out carbon dioxide. The energy released from transferring the electrons from high-energy states in NADH and quinol is conserved first as proton gradient and converted to ATP via ATP synthase. This generates an additional *28* molecules of ATP (24 from the 8 NADH + 4 from the 2 quinols), totaling to 32 molecules of ATP conserved per degraded glucose (two from glycolysis + two from the citrate cycle). It is clear that using oxygen to completely oxidize glucose provides an organism with far more energy than any oxygen-independent metabolic feature, and this is thought to be the reason why complex life appeared only after Earth's atmosphere accumulated large amounts of oxygen.

Gluconeogenesis

In vertebrates, vigorously contracting skeletal muscles (during weightlifting or sprinting, for example) do not receive enough oxygen to meet the energy demand, and so they shift to anaerobic metabolism, converting glucose to lactate. The liver regenerates the glucose, using a process called gluconeogenesis. This process is not quite the opposite of glycolysis, and actually requires three times the amount of energy gained from glycolysis (six molecules of ATP are used, compared to the two gained in glycolysis). Analogous to the above reactions, the glucose produced can then undergo glycolysis in tissues that need energy, be stored as glycogen (or starch in plants), or be converted to other monosaccharides or joined into di- or oligosaccharides. The combined pathways of glycolysis during exercise, lactate's crossing via the bloodstream to the liver, subsequent gluconeogenesis and release of glucose into the bloodstream is called the Cori cycle.

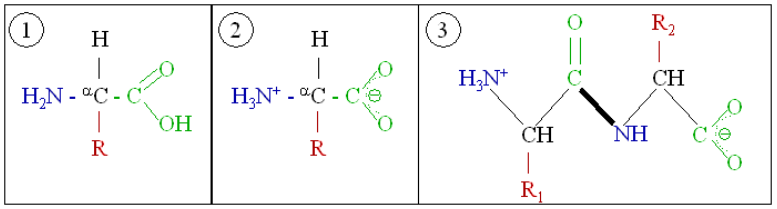
Proteins



A schematic of hemoglobin. The red and blue ribbons represent the protein globin; the green structures are the heme groups.

Like carbohydrates, some proteins perform largely structural roles. For instance, movements of the proteins actin and myosin ultimately are responsible for the contraction of skeletal muscle. One property many proteins have is that they specifically bind to a certain molecule or class of molecules—they may be *extremely* selective in what they bind. Antibodies are an example of proteins that attach to one specific type of molecule. In fact, the enzyme-linked immunosorbent assay (ELISA), which uses antibodies, is currently one of the most sensitive tests modern medicine uses to detect various biomolecules. Probably the most important proteins, however, are the enzymes. These molecules recognize specific reactant molecules called *substrates*; they then catalyze the reaction between them. By lowering the activation energy, the enzyme speeds up that reaction by a rate of 10^{11} or more: a reaction that would normally take over 3,000 years to complete spontaneously might take less than a second with an enzyme. The enzyme itself is not used up in the process, and is free to catalyze the same reaction with a new set of substrates. Using various modifiers, the activity of the enzyme can be regulated, enabling control of the biochemistry of the cell as a whole.

In essence, proteins are chains of amino acids. An amino acid consists of a carbon atom bound to four groups. One is an amino group, —NH_2, and one is a carboxylic acid group, —COOH (although these exist as —NH_3^+ and —COO^- under physiologic conditions). The third is a simple hydrogen atom. The fourth is commonly denoted "—R" and is different for each amino acid. There are twenty standard amino acids. Some of these have functions by themselves or in a modified form; for instance, glutamate functions as an important neurotransmitter.



Generic amino acids (1) in neutral form, (2) as they exist physiologically, and (3) joined together as a dipeptide.

Amino acids can be joined together via a peptide bond. In this dehydration synthesis, a water molecule is removed and the peptide bond connects the nitrogen of one amino acid's amino group to the carbon of the other's carboxylic acid group. The resulting molecule is called a *dipeptide*, and short stretches of amino acids (usually, fewer than around thirty) are called *peptides* or polypeptides. Longer stretches merit the title *proteins*. As an example, the important blood serum protein albumin contains 585 amino acid residues.

The structure of proteins is traditionally described in a hierarchy of four levels. The primary structure of a protein simply consists of its linear sequence of amino acids; for instance, "alanine-glycine-tryptophan-serine-glutamate-asparagine-glycine-lysine-…". Secondary structure is concerned with local morphology (morphology being the study of structure). Some combinations of amino acids will tend to curl up in a coil called an α-helix or into a sheet called a β-sheet; some α-helixes can be seen in the hemoglobin schematic above. Tertiary structure is the entire three-dimensional shape of the protein. This shape is determined by the sequence of amino acids. In fact, a single change can change the entire structure. The alpha chain of hemoglobin contains 146 amino acid residues; substitution of the glutamate residue at position 6 with a valine residue changes the behavior of hemoglobin so much that it results in sickle-cell disease. Finally quaternary structure is concerned with the structure of a protein with multiple peptide subunits, like hemoglobin with its four subunits. Not all proteins have more than one subunit.

Ingested proteins are usually broken up into single amino acids or dipeptides in the small intestine, and then absorbed. They can then be joined together to make new proteins. Intermediate products of glycolysis, the citric acid cycle, and the pentose phosphate pathway can be used to make all twenty amino acids, and most bacteria and plants possess all the necessary enzymes to synthesize them. Humans and other mammals, however, can only synthesize half of them. They cannot synthesize isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. These are the essential amino acids, since it is essential to ingest them. Mammals do possess the enzymes to synthesize alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, and tyrosine, the nonessential amino acids. While they can synthesize arginine and histidine, they cannot produce it in sufficient amounts for young, growing animals, and so these are often considered essential amino acids.

If the amino group is removed from an amino acid, it leaves behind a carbon skeleton called an α-keto acid. Enzymes called transaminases can easily transfer the amino group from one amino acid (making it an α-keto acid) to another α-keto acid (making it an amino acid). This is important in the biosynthesis of amino acids, as for many of the pathways, intermediates from other biochemical pathways are converted to the α-keto acid skeleton, and then an amino group is added, often via transamination. The amino acids may then be linked together to make a protein.

A similar process is used to break down proteins. It is first hydrolyzed into its component amino acids. Free ammonia (NH_3), existing as the ammonium ion (NH_4^+) in blood, is toxic to life forms. A suitable method for excreting it must therefore exist. Different strategies have evolved in different animals, depending on the animals' needs. Unicellular organisms, of course, simply release the ammonia into the environment. Similarly, bony fish can release the ammonia into the water where it is quickly diluted. In general, mammals convert the ammonia into urea,

via the urea cycle.

Lipids

The term lipid comprises a diverse range of molecules and to some extent is a catchall for relatively water-insoluble or nonpolar compounds of biological origin, including waxes, fatty acids, fatty-acid derived phospholipids, sphingolipids, glycolipids and terpenoids (e.g. retinoids and steroids). Some lipids are linear aliphatic molecules, while others have ring structures. Some are aromatic, while others are not. Some are flexible, while others are rigid.

Most lipids have some polar character in addition to being largely nonpolar. Generally, the bulk of their structure is nonpolar or hydrophobic ("water-fearing"), meaning that it does not interact well with polar solvents like water. Another part of their structure is polar or hydrophilic ("water-loving") and will tend to associate with polar solvents like water. This makes them amphiphilic molecules (having both hydrophobic and hydrophilic portions). In the case of cholesterol, the polar group is a mere -OH (hydroxyl or alcohol). In the case of phospholipids, the polar groups are considerably larger and more polar, as described below.

Lipids are an integral part of our daily diet. Most oils and milk products that we use for cooking and eating like butter, cheese, ghee etc., are composed of fats. Vegetable oils are rich in various polyunsaturated fatty acids (PUFA). Lipid-containing foods undergo digestion within the body and are broken into fatty acids and glycerol, which are the final degradation products of fats and lipids.

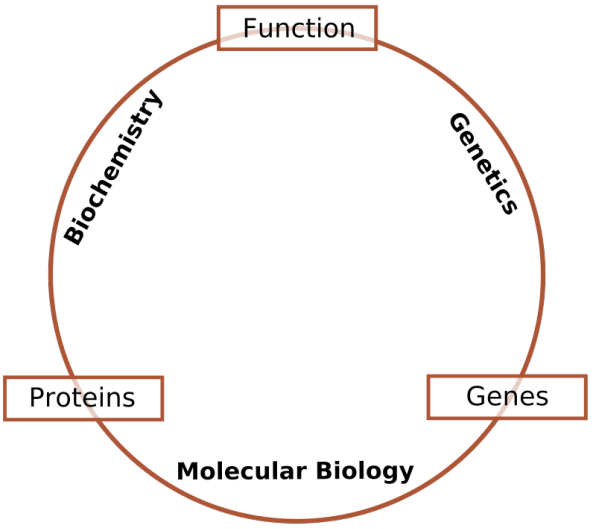
Nucleic acids

A nucleic acid is a complex, high-molecular-weight biochemical macromolecule composed of nucleotide chains that convey genetic information. The most common nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids are found in all living cells and viruses. Aside from the genetic material of the cell, nucleic acids often play a role as second messengers, as well as forming the base molecule for adenosine triphosphate, the primary energy-carrier molecule found in all living organisms.

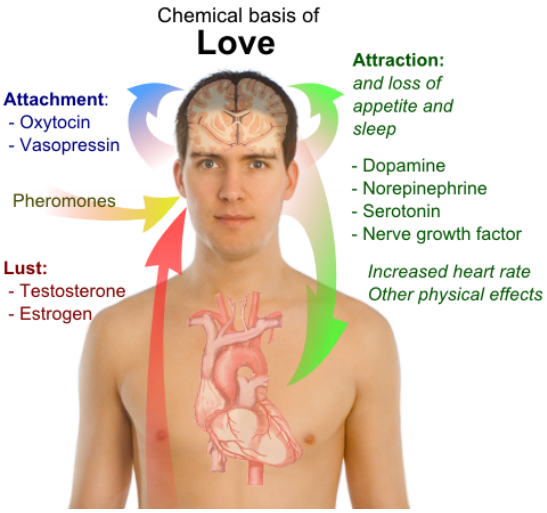
Nucleic acid, so called because of its prevalence in cellular nuclei, is the generic name of the family of biopolymers. The monomers are called nucleotides, and each consists of three components: a nitrogenous heterocyclic base (either a purine or a pyrimidine), a pentose sugar, and a phosphate group. Different nucleic acid types differ in the specific sugar found in their chain (e.g. DNA or deoxyribonucleic acid contains 2-deoxyriboses). Also, the nitrogenous bases possible in the two nucleic acids are different: adenine, cytosine, and guanine occur in both RNA and DNA, while thymine occurs only in DNA and uracil occurs in RNA.

Relationship to other "molecular-scale" biological sciences

Researchers in biochemistry use specific techniques native to biochemistry, but increasingly combine these with techniques and ideas from genetics, molecular biology and biophysics. There has never been a hard-line between these disciplines in terms of content and technique. Today the terms *molecular biology* and *biochemistry* are nearly interchangeable. The following figure is a schematic that depicts one possible view of the relationship between the fields:



Schematic relationship between biochemistry, genetics and molecular biology



Simplistic overview of the chemical basis of love, one of many applications that may be described in terms of biochemistry.

- *Biochemistry* is the study of the chemical substances and vital processes occurring in living organisms. Biochemists focus heavily on the role, function, and structure of biomolecules. The study of the chemistry behind biological processes and the synthesis of biologically active molecules are examples of biochemistry.
- *Genetics* is the study of the effect of genetic differences on organisms. Often this can be inferred by the absence of a normal component (e.g. one gene). The study of "mutants" – organisms which lack one or more functional components with respect to the so-called "wild type" or normal phenotype. Genetic interactions (epistasis) can often confound simple interpretations of such "knock-out" studies.
- *Molecular biology* is the study of molecular underpinnings of the process of replication, transcription and translation of the genetic material. The central dogma of molecular biology where genetic material is transcribed into RNA and then translated into protein, despite being an oversimplified picture of molecular biology, still provides a good starting point for understanding the field. This picture, however, is undergoing revision in light of emerging novel roles for RNA.
- *Chemical Biology* seeks to develop new tools based on small molecules that allow minimal perturbation of biological systems while providing detailed information about their function. Further, chemical biology employs biological systems to create non-natural hybrids between biomolecules and synthetic devices (for example emptied viral capsids that can deliver gene therapy or drug molecules).

See also

Lists

- List of biochemistry topics
- List of biochemists
- List of biomolecules
- List of geneticists & biochemists
- List of nucleic acid simulation software
- Important publications in biochemistry (biology)
- Important publications in biochemistry (chemistry)

Related topics

- Biological psychiatry
- Biophysics
- Carbon chauvinism
- Chemical ecology
- Computational biomodeling
- EC number
- Hypothetical types of biochemistry
- International Union of Biochemistry and Molecular Biology
- Metabolome
- Metabolomics
- Molecular biology
- Molecular medicine
- Plant biochemistry
- Structural biology
- Stoichiometry
- Small molecule
- Veterinary

Notes

a. It should be noted that fructose is not the only sugar found in fruits. Glucose and sucrose are also found in varying quantities in various fruits, and indeed sometimes exceed the fructose present. For example, 32 % of the edible portion of date is glucose, compared with 23.70 % fructose and 8.20 % sucrose. Conversely, peaches contain more sucrose (6.66 %) than they do fructose (0.93 %) or glucose (1.47 %).[5]

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Further reading

- Hunter, Graeme K. (2000). *Vital Forces: The Discovery of the Molecular Basis of Life*. San Diego: Academic Press. ISBN 0-12-361810-X. OCLC 162129355 191848148 44187710.

External links

- The Virtual Library of Biochemistry and Cell Biology (http://www.biochemweb.org/)
- Biochemistry, 5th ed. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=stryer.TOC&depth=2) Full text of Berg, Tymoczko, and Stryer, courtesy of NCBI.
- Biochemistry, 2nd ed. (http://www.web.virginia.edu/Heidi/home.htm) Full text of Garrett and Grisham.
- Biochemistry Animation (http://www.1lec.com/Biochemistry/) (Narrated Flash animations.)
- SystemsX.ch - The Swiss Initiative in Systems Biology (http://www.systemsX.ch/)
- Biochemistry Online Resources (http://www.icademic.org/97445/Biochemistry/) – Lists of Biochemistry departments, websites, journals, books and reviews, employment opportunities and events.

biochemical families: Carbohydrates (Glycosides, Alcohols) · Lipids (Steroids, Phospholipids, Glycolipids, Fatty acids, Tetrapyrroles) · Proteins (Amino acids, Peptides, Glycoproteins) · Nucleobases/Nucleic acids

Quantum biochemistry

Quantum chemistry is a branch of theoretical chemistry which applies quantum mechanics and quantum field theory to address problems in chemistry. One application of quantum chemistry is the electronic behavior of atoms and molecules relative to their chemical reactivity. Quantum chemistry lies on the border between chemistry and physics. Thus, significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale[1] , but can span from elementary particles such as electrons (fermions) and photons (bosons) to the cosmos such as star-formation[2] . It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

History

The history of quantum chemistry essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements ε such that each of these energy elements is proportional to the frequency ν with which they each individually radiate

energy, as defined by the following formula:

$$\epsilon = h\nu$$

where *h* is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic, or molecular systems, involve the motions of three or more "particles", their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.

Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen (H_2) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its significantly lower computational requirements (scaling typically no worse than n^3 with respect to n basis functions) allow it to tackle larger polyatomic molecules and even macromolecules. This computational affordability and often comparable accuracy to MP2 and CCSD (post-Hartree–Fock methods) has made it one of the most popular methods in computational chemistry at present.

Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework *molecular dynamics (MD)*. Statistical approaches, using for example Monte Carlo methods, are also possible.

Adiabatic chemical dynamics

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in 1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

Non-adiabatic chemical dynamics

Non-adiabatic dynamics consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagneton. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Molecular modelling
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

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[2] "Astrophysics and Astrochemistry". *Astrophysics and Astrochemistry*. (http://www.astrochemistry.eu/).

External links

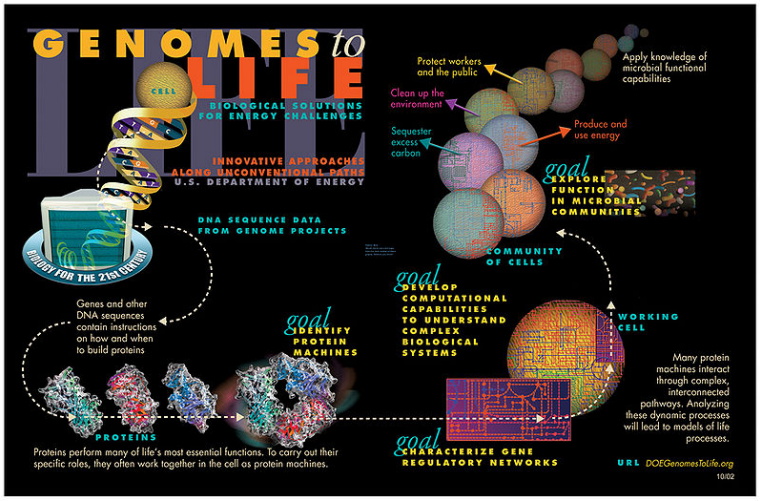
- The Sherrill Group - Notes (http://vergil.chemistry.gatech.edu/notes/index.html)
- ChemViz Curriculum Support Resources (http://www.shodor.org/chemviz/)
- Early ideas in the history of quantum chemistry (http://www.quantum-chemistry-history.com/)
- The Particle Adventure (http://particleadventure.org/)

Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture (http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.html)
- Rudolph Marcus' Nobel lecture (http://nobelprize.org/chemistry/laureates/1992/marcus-lecture.html)
- Robert Mulliken's Nobel lecture (http://nobelprize.org/chemistry/laureates/1966/mulliken-lecture.html)
- Linus Pauling's Nobel lecture (http://nobelprize.org/chemistry/laureates/1954/pauling-lecture.html)
- John Pople's Nobel lecture (http://nobelprize.org/chemistry/laureates/1998/pople-lecture.html)

Complex Systems Biology

Systems biology is a term used to describe a number of trends in bioscience research, and a movement which draws on those trends. Proponents describe systems biology as a biology-based inter-disciplinary study field that focuses on complex interactions in biological systems, claiming that it uses a new perspective (holism instead of reduction). Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. An often stated ambition of systems biology is the modeling and discovery of emergent properties, properties of a system whose theoretical description is only possible using techniques which fall under the remit of systems biology.



Example of systems biology research.

Overview

Systems biology can be considered from a number of different aspects:

- As a **field of study**, particularly, the study of the interactions between the components of *biological systems*, and how these interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway).[1] [2]
- As a **paradigm**, usually defined in antithesis to the so-called reductionist paradigm (biological organisation), although fully consistent with the scientific method. The distinction between the two paradigms is referred to in these quotations:

  "The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models" Science[3]

  "Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term" Denis Noble[4]
- As a series of **operational protocols used for performing research**, namely a cycle composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory.[5] [6] Since the objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore, transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.
- As the application of dynamical systems theory to molecular biology.
- As a **socioscientific phenomenon** defined by the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

This variety of viewpoints is illustrative of the fact that systems biology refers to a cluster of peripherally overlapping concepts rather than a single well-delineated field. However the term has widespread currency and popularity as of 2007, with chairs and institutes of systems biology proliferating worldwide.

History

Systems biology finds its roots in:

- the quantitative modeling of enzyme kinetics, a discipline that flourished between 1900 and 1970,
- the mathematical modeling of population growth,
- the simulations developed to study neurophysiology, and
- control theory and cybernetics.

One of the theorists who can be seen as one of the precursors of systems biology is Ludwig von Bertalanffy with his general systems theory [7] . One of the first numerical simulations in biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley, who constructed a mathematical model that explained the action potential propagating along the axon of a neuronal cell.[8] Their model described a cellular function emerging from the interaction between two different molecular components, a potassium and a sodium channels, and can therefore be seen as the beginning of computational systems biology.[9] In 1960, Denis Noble developed the first computer model of the heart pacemaker.[10]

The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology."[11] [12]

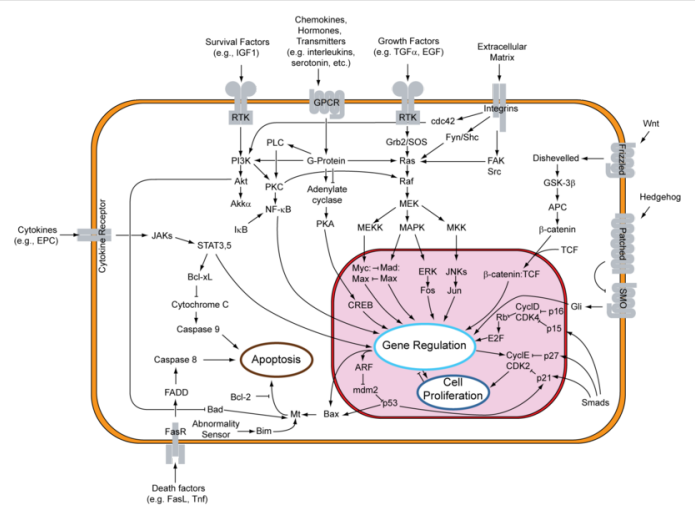
The 1960s and 1970s saw the development of several approaches to study complex molecular systems, such as the Metabolic Control Analysis and the biochemical systems theory. The successes of molecular biology throughout the 1980s, coupled with a skepticism toward theoretical biology, that then promised more than it achieved, caused the quantitative modelling of biological processes to become a somewhat minor field.

However the birth of functional genomics in the 1990s meant that large quantities of high quality data became available, while the computing power exploded, making more realistic models possible. In 1997, the group of Masaru Tomita published the first quantitative model of the metabolism of a whole (hypothetical) cell.

Around the year 2000, after Institutes of Systems Biology were established in Seattle and Tokyo, systems biology emerged as a movement in its own right, spurred on by the completion of various genome projects, the large increase in data from the omics (e.g. genomics and proteomics) and the accompanying advances in high-throughput experiments and bioinformatics. Since then, various research institutes dedicated to systems biology have been developed. As of summer 2006, due to a shortage of people in systems biology[13] several doctoral training centres in systems biology have been established in many parts of the world.

Disciplines associated with systems biology

According to the interpretation of Systems Biology as the ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools, some typical technology platforms are:



Overview of signal transduction pathways

- Phenomics: Organismal variation in phenotype as it changes during its life span..
- Genomics: Organismal deoxyribonucleic acid (DNA) sequence, including intra-organisamal cell specific variation. (i.e. Telomere length variation etc.).
- Epigenomics / Epigenetics: Organismal and corresponding cell specific transcriptomic regulating factors not empirically coded in the genomic sequence. (i.e. DNA methylation, Histone Acetelation etc.).
- Transcriptomics: Organismal, tissue or whole cell gene expression measurements by DNA microarrays or serial analysis of gene expression
- Interferomics: Organismal, tissue, or cell level transcript correcting factors (i.e. RNA interference)
- Translatomics / Proteomics: Organismal, tissue, or cell level measurements of proteins and peptides via two-dimensional gel electrophoresis, mass spectrometry or multi-dimensional protein identification techniques (advanced HPLC systems coupled with mass spectrometry). Sub disciplines include phosphoproteomics, glycoproteomics and other methods to detect chemically modified proteins.
- Metabolomics: Organismal, tissue, or cell level measurements of all small-molecules known as metabolites.
- Glycomics: Organismal, tissue, or cell level measurements of carbohydrates.
- Lipidomics: Organismal, tissue, or cell level measurements of lipids.

In addition to the identification and quantification of the above given molecules further techniques analyze the dynamics and interactions within a cell. This includes:

- Interactomics: Organismal, tissue, or cell level study of interactions between molecules. Currently the authoratative molecular discipline in this field of study is protein-protein interactions (PPI), although the working definition does not pre-clude inclusion of other molecular disciplines such as those defined here.
- Fluxomics: Organismal, tissue, or cell level measurements of molecular dynamic changes over time.
- Biomics: systems analysis of the biome.

The investigations are frequently combined with large scale perturbation methods, including gene-based (RNAi, mis-expression of wild type and mutant genes) and chemical approaches using small molecule libraries. Robots and automated sensors enable such large-scale experimentation and data acquisition. These technologies are still emerging and many face problems that the larger the quantity of data produced, the lower the quality. A wide variety of quantitative scientists (computational biologists, statisticians, mathematicians, computer scientists, engineers, and physicists) are working to improve the quality of these approaches and to create, refine, and retest the models to accurately reflect observations.

The systems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks.[14] [15] For instance, a cellular network can be modelled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Other aspects of computer science and informatics are also used in systems biology. These include new forms of computational model, such as the use of process calculi to model biological processes, the integration of information from the literature, using techniques of information extraction and text mining, the development of online databases and repositories for sharing data and models, approaches to database integration and software interoperability via loose coupling of software, websites and databases, or commercial suits, and the development of syntactically and semantically sound ways of representing biological models.

See also

Related fields

- Bioinformatics
- Biological network inference
- Biological systems engineering
- Biomedical cybernetics
- Biostatistics
- Computational biology
- Computational systems biology
- Complex systems
- Complex systems biology
- Extrapolation based molecular systems biology
- Theoretical Biophysics
- Network Biology
- Relational Biology
- Translational Research
- Scotobiology
- Synthetic biology
- Systems biology modeling
- Systems ecology
- Systems genetics
- Systems immunology

Related terms

- Life
- Biological organisation
- Artificial life
- Gene regulatory network
- Metabolic network modelling
- Living systems theory
- Network Theory of Aging
- Regulome
- Systems Biology Markup Language (SBML)
- Systems Biology Graphical Notation (SBGN)
- SBO
- Viable System Model
- Antireductionism

Systems biologists

- Category:Systems biologists

Lists

- Category:Systems biologists
- List of systems biology conferences
- List of omics topics in biology
- List of publications in systems biology
- List of systems biology research groups
- List of systems biology visualization software

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- BMC Systems Biology (http://www.biomedcentral.com/bmcsystbiol) - open access journal on systems biology
- Molecular Systems Biology (http://www.nature.com/msb) - open access journal on systems biology
- IET Systems Biology (http://www.ietdl.org/IET-SYB) - not open access journal on systems biology
- WIRES Systems Biology and Medicine (http://wires.wiley.com/WileyCDA/WiresJournal/wisId-WSBM.html) - open access review journal on systems biology and medicine
- EURASIP Journal on Bioinformatics and Systems Biology (http://www.hindawi.com/journals/bsb/)
- Systems and Synthetic Biology (http://www.springer.com/biomed/journal/11693)
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External links

- Institute for Systems Biology: SBI (http://www.systemsbiology.org)
- Applied BioDynamics Laboratory: Boston University (http://www.bu.edu/abl/)
- Institute for Research in Immunology and Cancer (IRIC): Université de Montréal (http://www.iric.ca)
- Systems Biology - BioChemWeb.org (http://www.biochemweb.org/systems.shtml)
- Systems Biology Portal (http://www.systems-biology.org/) - administered by the Systems Biology Institute
- Semantic Systems Biology (http://www.semantic-systems-biology.org)
- SystemsX.ch (http://www.systemsx.ch/) - The Swiss Initiative in Systems Biology
- Systems Biology at the Pacific Northwest National Laboratory (http://www.sysbio.org/)
- Institute of Bioinformatics and Systems Biology (http://bioinfo.nctu.edu.tw/), National Chiao Tung University, Taiwan

Complexity

In general usage, **complexity** tends to be used to characterize something with many parts in intricate arrangement. The study of these complex linkages is the main goal of network theory and network science. In science there are at this time a number of approaches to characterizing complexity, many of which are reflected in this article. In a business context, complexity management is the methodology to minimize value-destroying complexity and efficiently control value-adding complexity in a cross-functional approach.

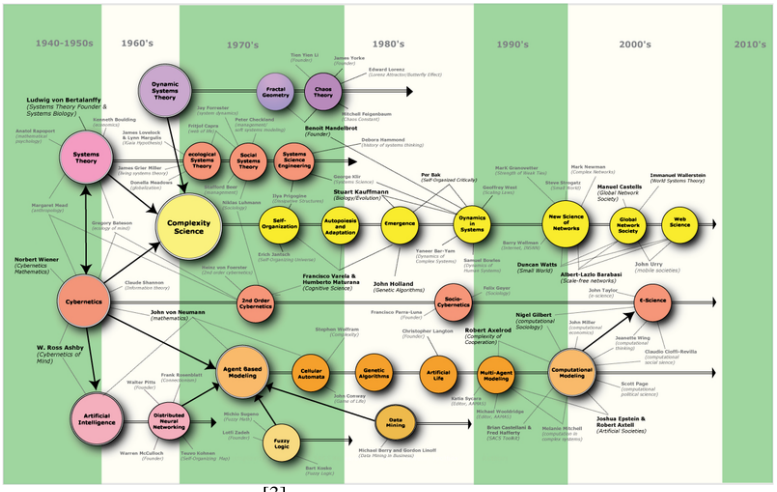
Definitions are often tied to the concept of a "system"—a set of parts or elements which have relationships among them differentiated from relationships with other elements outside the relational regime. Many definitions tend to postulate or assume that complexity expresses a condition of numerous elements in a system and numerous forms of relationships among the elements. At the same time, what is complex and what is simple is relative and changes with time.

Some definitions key on the question of the probability of encountering a given condition of a system once characteristics of the system are specified. Warren Weaver has posited that the complexity of a particular system is the degree of difficulty in predicting the properties of the system if the properties of the system's parts are given. In Weaver's view, complexity comes in two forms: disorganized complexity, and organized complexity.[1] Weaver's paper has influenced contemporary thinking about complexity.[2]

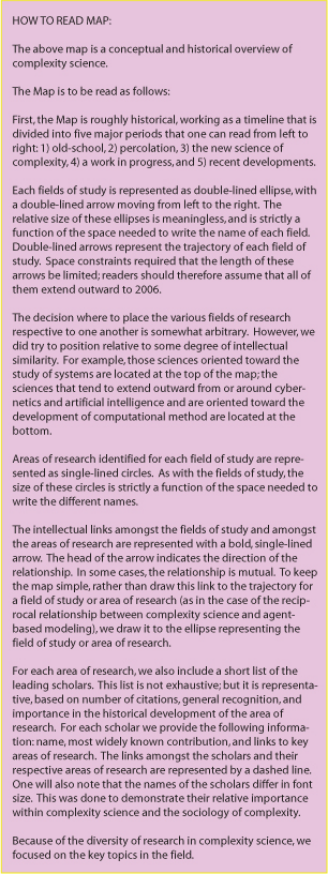
The approaches which embody concepts of systems, multiple elements, multiple relational regimes, and state spaces might be summarized as implying that complexity arises from the number of distinguishable relational regimes (and their associated state spaces) in a defined system.

Some definitions relate to the algorithmic basis for the expression of a complex phenomenon or model or mathematical expression, as is later set out herein.

Disorganized complexity vs. organized complexity



Map of Complexity Science [3]. The web version of this map provides internet links to many of the leading scholars and areas of research in complexity science.



HOW TO READ MAP:

The above map is a conceptual and historical overview of complexity science.

The Map is to be read as follows:

First, the Map is roughly historical, working as a timeline that is divided into five major periods that one can read from left to right: 1) old-school, 2) percolation, 3) the new science of complexity, 4) a work in progress, and 5) recent developments.

Each fields of study is represented as double-lined ellipse, with a double-lined arrow moving from left to the right. The relative size of these ellipses is meaningless, and is strictly a function of the space needed to write the name of each field. Double-lined arrows represent the trajectory of each field of study. Space constraints required that the length of these arrows be limited; readers should therefore assume that all of them extend outward to 2006.

The decision where to place the various fields of research respective to one another is somewhat arbitrary. However, we did try to position relative to some degree of intellectual similarity. For example, those sciences oriented toward the study of systems are located at the top of the map; the sciences that tend to extend outward from or around cybernetics and artificial intelligence and are oriented toward the development of computational method are located at the bottom.

Areas of research identified for each field of study are represented as single-lined circles. As with the fields of study, the size of these circles is strictly a function of the space needed to write the different names.

The intellectual links amongst the fields of study and amongst the areas of research are represented with a bold, single-lined arrow. The head of the arrow indicates the direction of the relationship. In some cases, the relationship is mutual. To keep the map simple, rather than draw this link to the trajectory for a field of study or area of research (as in the case of the reciprocal relationship between complexity science and agent-based modeling), we draw it to the ellipse representing the field of study or area of research.

For each area of research, we also include a short list of the leading scholars. This list is not exhaustive; but it is representative, based on number of citations, general recognition, and importance in the historical development of the area of research. For each scholar we provide the following information: name, most widely known contribution, and links to key areas of research. The links amongst the scholars and their respective areas of research are represented by a dashed line. One will also note that the names of the scholars differ in font size. This was done to demonstrate their relative importance within complexity science and the sociology of complexity.

Because of the diversity of research in complexity science, we focused on the key topics in the field.

Map legend

One of the problems in addressing complexity issues has been distinguishing conceptually between the large number of variances in relationships extant in random collections, and the sometimes large, but smaller, number of relationships between elements in systems where constraints (related to correlation of otherwise independent elements) simultaneously reduce the variations from element independence and create distinguishable regimes of more-uniform, or correlated, relationships, or interactions.

Weaver perceived and addressed this problem, in at least a preliminary way, in drawing a distinction between "disorganized complexity" and "organized complexity".

In Weaver's view, disorganized complexity results from the particular system having a very large number of parts, say millions of parts, or many more. Though the interactions of the parts in a "disorganized complexity" situation can be seen as largely random, the properties of the system as a whole can be understood by using probability and statistical methods.

A prime example of disorganized complexity is a gas in a container, with the gas molecules as the parts. Some would suggest that a system of disorganized complexity may be compared, for example, with the (relative) simplicity of the planetary orbits—the latter can be known by applying Newton's laws of motion, though this example involved highly correlated events.

Organized complexity, in Weaver's view, resides in nothing else than the non-random, or correlated, interaction between the parts. These correlated relationships create a differentiated structure which can, as a system, interact with other systems. The coordinated system manifests properties not carried by, or dictated by, individual parts. The

organized aspect of this form of complexity vis a vis other systems than the subject system can be said to "emerge," without any "guiding hand".

The number of parts does not have to be very large for a particular system to have emergent properties. A system of organized complexity may be understood in its properties (behavior among the properties) through modeling and simulation, particularly modeling and simulation with computers. An example of organized complexity is a city neighborhood as a living mechanism, with the neighborhood people among the system's parts.[4]

Sources and factors of complexity

The source of disorganized complexity is the large number of parts in the system of interest, and the lack of correlation between elements in the system.

There is no consensus at present on general rules regarding the sources of organized complexity, though the lack of randomness implies correlations between elements. See e.g. Robert Ulanowicz's treatment of ecosystems.[5] Consistent with prior statements here, the number of parts (and types of parts) in the system and the number of relations between the parts would have to be non-trivial—however, there is no general rule to separate "trivial" from "non-trivial".

Complexity of an object or system is a relative property. For instance, for many functions (problems), such a computational complexity as time of computation is smaller when multitape Turing machines are used than when Turing machines with one tape are used. Random Access Machines allow one to even more decrease time complexity (Greenlaw and Hoover 1998: 226), while inductive Turing machines can decrease even the complexity class of a function, language or set (Burgin 2005). This shows that tools of activity can be an important factor of complexity.

Specific meanings of complexity

In several scientific fields, "complexity" has a specific meaning :

- In computational complexity theory, the amounts of resources required for the execution of algorithms is studied. The most popular types of computational complexity are the time complexity of a problem equal to the number of steps that it takes to solve an instance of the problem as a function of the size of the input (usually measured in bits), using the most efficient algorithm, and the space complexity of a problem equal to the volume of the memory used by the algorithm (e.g., cells of the tape) that it takes to solve an instance of the problem as a function of the size of the input (usually measured in bits), using the most efficient algorithm. This allows to classify computational problems by complexity class (such as P, NP ...). An axiomatic approach to computational complexity was developed by Manuel Blum. It allows one to deduce many properties of concrete computational complexity measures, such as time complexity or space complexity, from properties of axiomatically defined measures.
- In algorithmic information theory, the *Kolmogorov complexity* (also called *descriptive complexity*, *algorithmic complexity* or *algorithmic entropy*) of a string is the length of the shortest binary program which outputs that string. Different kinds of Kolmogorov complexity are studied: the uniform complexity, prefix complexity, monotone complexity, time-bounded Kolmogorov complexity, and space-bounded Kolmogorov complexity. An axiomatic approach to Kolmogorov complexity based on Blum axioms (Blum 1967) was introduced by Mark Burgin in the paper presented for publication by Andrey Kolmogorov (Burgin 1982). The axiomatic approach encompasses other approaches to Kolmogorov complexity. It is possible to treat different kinds of Kolmogorov complexity as particular cases of axiomatically defined generalized Kolmogorov complexity. Instead, of proving similar theorems, such as the basic invariance theorem, for each particular measure, it is possible to easily deduce all such results from one corresponding theorem proved in the axiomatic setting. This is a general advantage of the axiomatic approach in mathematics. The axiomatic approach to Kolmogorov complexity was further

developed in the book (Burgin 2005) and applied to software metrics (Burgin and Debnath, 2003; Debnath and Burgin, 2003).

- In information processing, complexity is a measure of the total number of properties transmitted by an object and detected by an observer. Such a collection of properties is often referred to as a state.
- In business, complexity describes the variances and their consequences in various fields such as product portfolio, technologies, markets and market segments, locations, manufacturing network, customer portfolio, IT systems, organization, processes etc.
- In physical systems, complexity is a measure of the probability of the state vector of the system. This should not be confused with entropy; it is a distinct mathematical measure, one in which two distinct states are never conflated and considered equal, as is done for the notion of entropy statistical mechanics.
- In mathematics, Krohn-Rhodes complexity is an important topic in the study of finite semigroups and automata.
- In software engineering, programming complexity is a measure of the interactions of the various elements of the software. This differs from the computational complexity described above in that it is a measure of the design of the software.

There are different specific forms of complexity:

- In the sense of how complicated a problem is from the perspective of the person trying to solve it, limits of complexity are measured using a term from cognitive psychology, namely the hrair limit.
- Complex adaptive system denotes systems which have some or all of the following attributes[6]
  - The number of parts (and types of parts) in the system and the number of relations between the parts is non-trivial – however, there is no general rule to separate "trivial" from "non-trivial";
  - The system has memory or includes feedback;
  - The system can adapt itself according to its history or feedback;
  - The relations between the system and its environment are non-trivial or non-linear;
  - The system can be influenced by, or can adapt itself to, its environment; and
  - The system is highly sensitive to initial conditions.

Study of complexity

Complexity has always been a part of our environment, and therefore many scientific fields have dealt with complex systems and phenomena. Indeed, some would say that only what is somehow complex—what displays variation without being random—is worthy of interest.

The use of the term complex is often confused with the term complicated. In today's systems, this is the difference between myriad connecting "stovepipes" and effective "integrated" solutions.[7] This means that complex is the opposite of independent, while complicated is the opposite of simple.

While this has led some fields to come up with specific definitions of complexity, there is a more recent movement to regroup observations from different fields to study complexity in itself, whether it appears in anthills, human brains, or stock markets. One such interndisciplinary group of fields is relational order theories.

Complexity topics

Complex behaviour

The behaviour of a complex system is often said to be due to emergence and self-organization. Chaos theory has investigated the sensitivity of systems to variations in initial conditions as one cause of complex behaviour.

Complex mechanisms

Recent developments around artificial life, evolutionary computation and genetic algorithms have led to an increasing emphasis on complexity and complex adaptive systems.

Complex simulations

In social science, the study on the emergence of macro-properties from the micro-properties, also known as macro-micro view in sociology. The topic is commonly recognized as social complexity that is often related to the use of computer simulation in social science, i.e.: computational sociology.

Complex systems

Systems theory has long been concerned with the study of complex systems (In recent times, *complexity theory* and *complex systems* have also been used as names of the field). These systems can be biological, economic, technological, etc. Recently, complexity is a natural domain of interest of the real world socio-cognitive systems and emerging systemics research. Complex systems tend to be high-dimensional, non-linear and hard to model. In specific circumstances they may exhibit low dimensional behaviour.

Complexity in data

In information theory, algorithmic information theory is concerned with the complexity of strings of data.

Complex strings are harder to compress. While intuition tells us that this may depend on the codec used to compress a string (a codec could be theoretically created in any arbitrary language, including one in which the very small command "X" could cause the computer to output a very complicated string like "18995316"), any two Turing-complete languages can be implemented in each other, meaning that the length of two encodings in different languages will vary by at most the length of the "translation" language—which will end up being negligible for sufficiently large data strings.

These algorithmic measures of complexity tend to assign high values to random noise. However, those studying complex systems would not consider randomness as complexity.

Information entropy is also sometimes used in information theory as indicative of complexity.

Applications of complexity

Computational complexity theory is the study of the complexity of problems—that is, the difficulty of solving them. Problems can be classified by complexity class according to the time it takes for an algorithm—usually a computer program—to solve them as a function of the problem size. Some problems are difficult to solve, while others are easy. For example, some difficult problems need algorithms that take an exponential amount of time in terms of the size of the problem to solve. Take the travelling salesman problem, for example. It can be solved in time $O(n^2 2^n)$ (where *n* is the size of the network to visit—let's say the number of cities the travelling salesman must visit exactly once). As the size of the network of cities grows, the time needed to find the route grows (more than) exponentially.
Even though a problem may be computationally solvable in principle, in actual practice it may not be that simple. These problems might require large amounts of time or an inordinate amount of space. Computational complexity may be approached from many different aspects. Computational complexity can be investigated on the basis of time,

memory or other resources used to solve the problem. Time and space are two of the most important and popular considerations when problems of complexity are analyzed.

There exist a certain class of problems that although they are solvable in principle they require so much time or space that it is not practical to attempt to solve them. These problems are called intractable.

There is another form of complexity called hierarchical complexity. It is orthogonal to the forms of complexity discussed so far, which are called horizontal complexity

See also

- Chaos theory
- Command and Control Research Program
- Complexity theory (disambiguation page)
- Cyclomatic complexity
- Digital morphogenesis
- Evolution of complexity
- Game complexity
- Holism in science
- Interconnectedness
- Model of Hierarchical Complexity
- Names of large numbers
- Network science
- Network theory
- Novelty theory
- Occam's razor
- Process architecture
- Programming Complexity
- Sociology and complexity science
- Systems theory
- Variety (cybernetics)
- Volatility, uncertainty, complexity and ambiguity

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External links

- Quantifying Complexity Theory (http://www.calresco.org/lucas/quantify.htm) – classification of complex systems
- Complexity Measures (http://cscs.umich.edu/~crshalizi/notebooks/complexity-measures.html) – an article about the abundance of not-that-useful complexity measures.
- UC Four Campus Complexity Videoconferences (http://eclectic.ss.uci.edu/~drwhite/center/cac.html) – Human Sciences and Complexity
- Complexity Digest (http://comdig.unam.mx/) – networking the complexity community
- The Santa Fe Institute (http://www.santafe.edu/) – engages in research in complexity related topics
- Exploring Complexity in Science and Technology (http://web.cecs.pdx.edu/~mm/ExploringComplexityFall2009/index.html) – A introductory course about complex system by Melanie Mitchell

Complex adaptive system

Complex adaptive systems are special cases of complex systems. They are *complex* in that they are dynamic networks of interactions and relationships not aggregations of static entities. They are adaptive in that their individual and collective behaviour changes as a result of experience.[1]

Overview

The term *complex adaptive systems*, or *complexity science*, is often used to describe the loosely organized academic field that has grown up around the study of such systems. Complexity science is not a single theory— it encompasses more than one theoretical framework and is highly interdisciplinary, seeking the answers to some fundamental questions about living, adaptable, changeable systems.

Examples of complex adaptive systems include the stock market, social insect and ant colonies, the biosphere and the ecosystem, the brain and the immune system, the cell and the developing embryo, manufacturing businesses and any human social group-based endeavour in a cultural and social system such as political parties or communities. There are close relationships between the field of CAS and artificial life. In both areas the principles of emergence and self-organization are very important.

The ideas and models of CAS are essentially evolutionary, grounded in modern chemistry, biological views on adaptation, exaptation and evolution and simulation models in economics and social systems.

Definitions

A CAS is a complex, self-similar collection of interacting adaptive agents. The study of CAS focuses on complex, emergent and macroscopic properties of the system. Various definitions have been offered by different researchers:

- John H. Holland

  > A Complex Adaptive System (CAS) is a dynamic network of many agents (which may represent cells, species, individuals, firms, nations) acting in parallel, constantly acting and reacting to what the other agents are doing. The control of a CAS tends to be highly dispersed and decentralized. If there is to be any coherent behavior in the system, it has to arise from competition and cooperation among the agents themselves. The overall behavior of the system is the result of a huge number of decisions made every moment by many individual agents.[2]
  >
  > A CAS behaves/evolves according to three key principles: order is emergent as opposed to predetermined (c.f. Neural Networks), the system's history is irreversible, and the system's future is often unpredictable. The basic building blocks of the CAS are agents. Agents scan their environment and develop schema representing

interpretive and action rules. These schema are subject to change and evolution.[3]

- Other definitions

  Macroscopic collections of simple (and typically nonlinear) interacting units that are endowed with the ability to evolve and adapt to a changing environment.[4]

General properties

What distinguishes a CAS from a pure multi-agent system (MAS) is the focus on top-level properties and features like self-similarity, complexity, emergence and self-organization. A MAS is simply defined as a system composed of multiple interacting agents. In CASs, the agents as well as the system are adaptive: the system is self-similar. A CAS is a complex, self-similar collectivity of interacting adaptive agents. Complex Adaptive Systems are characterised by a high degree of adaptive capacity, giving them resilience in the face of perturbation.

Other important properties are adaptation (or homeostasis), communication, cooperation, specialization, spatial and temporal organization, and of course reproduction. They can be found on all levels: cells specialize, adapt and reproduce themselves just like larger organisms do. Communication and cooperation take place on all levels, from the agent to the system level. The forces driving co-operation between agents in such a system can, in some cases be analysed with game theory.

Characteristics

Complex adaptive systems are characterised as follows[5] and the most important are:

- The number of elements is sufficiently large that a conventional description (e.g. a system of differential equations) are not only impractical, but cease to assist in understanding the system, the elements also have to interact and the interaction must be dynamic. Interactions can be physical or involve the exchange of information.
- Such interactions are rich, i.e. any element in the system is affected and affects several other systems.
- The interactions are non-linear which means that small causes can have large results.
- Interactions are primarily but not exclusively with immediate neighbours and the nature of the influence is modulated.
- Any interaction can feed back onto itself directly or after a number of intervening stages, such feedback can vary in quality. The is known as *recurrency*.
- Such systems are open and it may be difficult or impossible to define system boundaries
- Complex systems operate under far from equilibrium conditions, there has to be a constant flow of energy to maintain the organisation of the system
- All complex systems have a history, they evolve and their past is co-responsible for their present behaviour
- Elements in the system are ignorant of the behaviour of the system as a whole responding only to what is available to it locally

Axelrod & Cohen [6] identify a series of key terms from a modeling perspective:

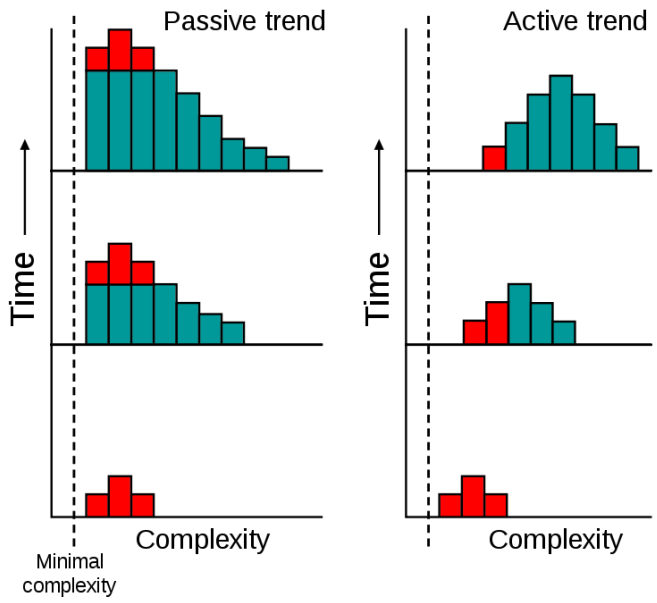
- **Strategy**, a conditional action pattern that indicates what to do in which circumstances
- **Artifact**, a material resource that has definite location and can respond to the action of agents
- **Agent**, a collection of properties, strategies & capabilities for interacting with artifacts & other agents
- **Population**, a collection of agents, or, in some situations, collections of strategies
- **System**, a larger collection, including one or more populations of agents and possibly also artifacts.
- **Type**, all the agents (or strategies) in a population that have some characteristic in common
- **Variety**, the diversity of types within a population or system
- **Interaction pattern**, the recurring regularities of contact among types within a system
- **Space (physical)**, location in geographical space & time of agents and artifacts
- **Space (conceptual)**, “location” in a set of categories structured so that “nearby” agents will tend to interact
- **Selection**, processes that lead to an increase or decrease in the frequency of various types of agent or strategies

- **Success criteria** or **performance measures**, a “score” used by an agent or designer in attributing credit in the selection of relatively successful (or unsuccessful) strategies or agents.

Evolution of complexity

Living organisms are complex adaptive systems. Although complexity is hard to quantify in biology, evolution has produced some remarkably complex organisms.[7] This observation has led to the common misconception of evolution being progressive and leading towards what are viewed as "higher organisms".[8]

If this were generally true, evolution would possess an active trend towards complexity. As shown below, in this type of process the value of the most common amount of complexity would increase over time.[9] Indeed, some artificial life simulations have suggested that the generation of CAS is an inescapable feature of evolution.[10] [11]



Passive versus active trends in the evolution of complexity. CAS at the beginning of the processes are colored red. Changes in the number of systems are shown by the height of the bars, with each set of graphs moving up in a time series.

However, the idea of a general trend towards complexity in evolution can also be explained through a passive process.[9] This involves an increase in variance but the most common value, the mode, does not change. Thus, the maximum level of complexity increases over time, but only as an indirect product of there being more organisms in total. This type of random process is also called a bounded random walk.

In this hypothesis, the apparent trend towards more complex organisms is an illusion resulting from concentrating on the small number of large, very complex organisms that inhabit the right-hand tail of the complexity distribution and ignoring simpler and much more common organisms. This passive model emphasizes that the overwhelming majority of species are microscopic prokaryotes,[12] which comprise about half the world's biomass[13] and constitute the vast majority of Earth's biodiversity.[14] Therefore, simple life remains dominant on Earth, and complex life appears more diverse only because of sampling bias.

This lack of an overall trend towards complexity in biology does not preclude the existence of forces driving systems towards complexity in a subset of cases. These minor trends are balanced by other evolutionary pressures that drive systems towards less complex states.

See also

- Agent-based model
- Artificial life
- Center for Complex Systems and Brain Sciences
- Center for Social Dynamics & Complexity (CSDC) at Arizona State University [15]
- Cognitive Science
- Command and Control Research Program
- Complex system
- Computational Sociology
- Enterprise systems engineering
- Generative sciences
- Santa Fe Institute
- Simulated reality
- Sociology and complexity science
- Swarm Development Group

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External links

- Complexity Digest (http://www.comdig.org/) comprehensive digest of latest CAS related news and research.
- DNA Wales Research Group (http://www.dnawales.co.uk/) Current Research in Organisational change CAS/CES related news and free research data. Also linked to the Business Doctor & BBC documentary series
- A description (http://pespmc1.vub.ac.be/CAS.html) of complex adaptive systems on the Principia Cybernetica Web.
- Quick reference (http://bactra.org/notebooks/complexity.html) single-page description of the 'world' of complexity and related ideas hosted by the Center for the Study of Complex Systems at the University of Michigan.
- Complex systems research network (http://www.complexsystems.net.au/)
- The Open Agent-Based Modeling Consortium (http://www.openabm.org/site/)

Computational biology

Computational biology is an interdisciplinary field that applies the techniques of computer science, applied mathematics and statistics to address biological problems. The main focus lies in the development of computational and statistical data analysis methods and in developing mathematical modeling and computational simulation techniques. By these means it addresses scientific research topics with their theoretical and experimental questions without a laboratory. It is connected to the following fields:

- Computational biomodeling, a field concerned with building computer models of biological systems.
- Bioinformatics, which applies algorithms and statistical techniques to the interpretation, classification and understanding of biological datasets. These typically consist of large numbers of DNA, RNA, or protein sequences. Sequence alignment is used to assemble the datasets for analysis. Comparisons of homologous sequences, gene finding, and prediction of gene expression are the most common techniques used on assembled datasets; however, analysis of such datasets have many applications throughout all fields of biology.
- Mathematical biology aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools.
- Computational genomics, a field within genomics which studies the genomes of cells and organisms. High-throughput genome sequencing produces lots of data, which requires extensive post-processing (genome assembly) and uses DNA microarray technologies to perform statistical analyses on the genes expressed in individual cell types. This can help find genes of interest for certain diseases or conditions. This field also studies the mathematical foundations of sequencing.
- Molecular modeling, which consists of modelling the behaviour of molecules of biological importance.
- Protein structure prediction and structural genomics, which attempt to systematically produce accurate structural models for three-dimensional protein structures that have not been determined experimentally.
- Computational biochemistry and biophysics, which make extensive use of structural modeling and simulation methods such as molecular dynamics and Monte Carlo method-inspired Boltzmann sampling methods in an attempt to elucidate the kinetics and thermodynamics of protein functions.

Biostatistics

Biostatistics (a contraction of biology and statistics; sometimes referred to as **biometry** or **biometrics**) is the application of statistics to a wide range of topics in biology. The science of biostatistics encompasses the design of biological experiments, especially in medicine and agriculture; the collection, summarization, and analysis of data from those experiments; and the interpretation of, and inference from, the results.

Biostatistics and the history of biological thought

Biostatistical reasoning and modeling were of critical importance to the foundation theories of modern biology. In the early 1900s, after the rediscovery of Mendel's work, the conceptual gaps in understanding between genetics and evolutionary Darwinism led to vigorous debate between biometricians such as Walter Weldon and Karl Pearson and Mendelians such as Charles Davenport, William Bateson and Wilhelm Johannsen. By the 1930s statisticians and models built on statistical reasoning had helped to resolve these differences and to produce the neo-Darwinian modern evolutionary synthesis.

The leading figures in the establishment of this synthesis all relied on statistics and developed its use in biology.

- Sir Ronald A. Fisher developed several basic statistical methods in support of his work *The Genetical Theory of Natural Selection*
- Sewall G. Wright used statistics in the development of modern population genetics
- J. B. S Haldane's book, *The Causes of Evolution*, reestablished natural selection as the premier mechanism of evolution by explaining it in terms of the mathematical consequences of Mendelian genetics.

These individuals and the work of other biostatisticians, mathematical biologists, and statistically inclined geneticists helped bring together evolutionary biology and genetics into a consistent, coherent whole that could begin to be quantitatively modeled.

In parallel to this overall development, the pioneering work of D'Arcy Thompson in *On Growth and Form* also helped to add quantitative discipline to biological study.

Despite the fundamental importance and frequent necessity of statistical reasoning, there may nonetheless have been a tendency among biologists to distrust or deprecate results which are not qualitatively apparent. One anecdote describes Thomas Hunt Morgan banning the Friden calculator from his department at Caltech, saying "Well, I am like a guy who is prospecting for gold along the banks of the Sacramento River in 1849. With a little intelligence, I can reach down and pick up big nuggets of gold. And as long as I can do that, I'm not going to let any people in my department waste scarce resources in placer mining."[1] Educators are now adjusting their curricula to focus on more quantitative concepts and tools.[2]

Education and training programs

Almost all educational programmes in biostatistics are at postgraduate level. They are most often found in schools of public health, affiliated with schools of medicine, forestry, or agriculture or as a focus of application in departments of statistics.

In the United States, while several universities have dedicated biostatistics departments, many other top-tier universities integrate biostatistics faculty into statistics or other departments, such as epidemiology. Thus departments carrying the name "biostatistics" may exist under quite different structures. For instance, relatively new biostatistics departments have been founded with a focus on bioinformatics and computational biology, whereas older departments, typically affiliated with schools of public health, will have more traditional lines of research involving epidemiological studies and clinical trials as well as bioinformatics. In larger universities where both a statistics and a biostatistics department exist, the degree of integration between the two departments may range from

the bare minimum to very close collaboration. In general, the difference between a statistics program and a biostatistics one is twofold: (i) statistics departments will often host theoretical/methodological research which are less common in biostatistics programs and (ii) statistics departments have lines of research that may include biomedical applications but also other areas such as industry (quality control), business and economics and biological areas other than medicine.

Applications of biostatistics

- Public health, including epidemiology, health services research, nutrition, and environmental health
- Design and analysis of clinical trials in medicine
- Population genetics, and statistical genetics in order to link variation in genotype with a variation in phenotype. This has been used in agriculture to improve crops and farm animals (animal breeding). In biomedical research, this work can assist in finding candidates for gene alleles that can cause or influence predisposition to disease in human genetics
- Anaysis of genomics data, for example from microarray or proteomics experiments [3] [4] . Often concerning diseases or disease stages [5] .
- Ecology, ecological forecasting
- Biological sequence analysis [6]
- Systems biology for gene network inference or pathways analysis

Statistical methods are beginning to be integrated into medical informatics, public health informatics, bioinformatics and computational biology.

Biostatistics journals

- *Biometrics*
- *Biometrika*
- *Biostatistics*
- *International Journal of Biostatistics, The*
- *Canadian Journal of Epidemiology and Biostatistics* [7]
- *Journal of Agricultural, Biological, and Environmental Statistics*
- *Journal of Biopharmaceutical Statistics*
- *Pharmaceutical Statistics*
- *Statistical Applications in Genetics and Molecular Biology*
- *Statistics in Biopharmaceutical Research*
- *Statistics in Medicine*
- *Turkiye Klinikleri Journal of Biostatistics*

Related fields

Biostatistics shares several methods with quantitative fields such as:

- computational biology
- computer science,
- operations research,
- psychometrics,
- statistics,
- econometrics, and
- mathematical demography

See also

- Ecological forecasting
- Group size measures
- Machine Learning
- Network Biology
- Quantitative parasitology
- Systems Biology

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[3] Helen Causton, John Quackenbush and Alvis Brazma (2003). "Statistical Analysis of Gene Expression Microarray Data". Wiley-Blackwell.
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[6] Warren J. Ewens and Gregory R. Grant (2004). "Statistical Methods in Bioinformatics: An Introduction". Springer.
[7] http://www.cjeb.ca/

External links

- The International Biometric Society (http://www.tibs.org)
- The Collection of Biostatistics Research Archive (http://www.biostatsresearch.com/repository/)
- Guide to Biostatistics (MedPageToday.com) (http://www.medpagetoday.com/Medpage-Guide-to-Biostatistics.pdf)
- Biostatistician (http://biostatistician.eu)

Journals

- Statistical Applications in Genetics and Molecular Biology (http://www.bepress.com/sagmb/)
- Statistics in Medicine (http://www3.interscience.wiley.com/cgi-bin/jhome/2988)
- The International Journal of Biostatistics (http://www.bepress.com/ijb/)
- Journal of Agricultural, Biological, and Environmental Statistics (http://www.amstat.org/publications/jabes/)
- Journal of Biopharmaceutical Statistics (http://www.tandf.co.uk/journals/titles/10543406.asp)
- Biostatistics (http://www.biostatistics.oxfordjournals.org/)
- Biometrics (http://www.tibs.org/biometrics/)
- Biometrika (http://biomet.oxfordjournals.org/)
- Biometrical Journal (http://www.biometrical-journal.de/)
- Genetics Selection Evolution (http://www.gse-journal.org/)

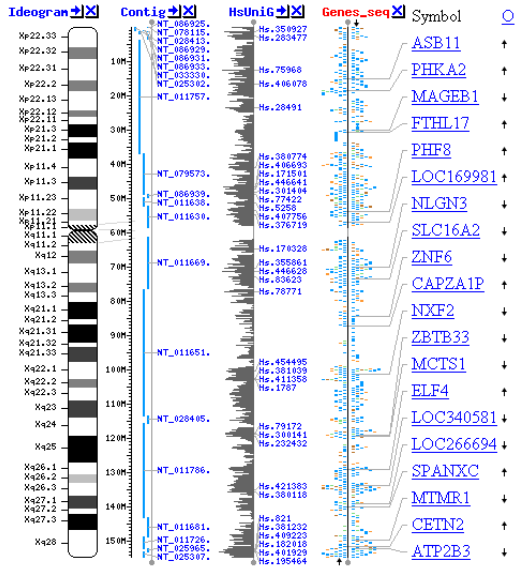
Bioinformatics

Bioinformatics is the application of statistics and computer science to the field of molecular biology.

The term *bioinformatics* was coined by Paulien Hogeweg in 1979 for the study of informatic processes in biotic systems. Its primary use since at least the late 1980s has been in genomics and genetics, particularly in those areas of genomics involving large-scale DNA sequencing.

Bioinformatics now entails the creation and advancement of databases, algorithms, computational and statistical techniques and theory to solve formal and practical problems arising from the management and analysis of biological data.

Over the past few decades rapid developments in genomic and other molecular research technologies and developments in information technologies have combined to produce a tremendous amount of information related to molecular biology. It is the name given to these mathematical and computing approaches used to glean understanding of biological processes.



Map of the human X chromosome (from the NCBI website). Assembly of the human genome is one of the greatest achievements of bioinformatics.

Common activities in bioinformatics include mapping and analyzing DNA and protein sequences, aligning different DNA and protein sequences to compare them and creating and viewing 3-D models of protein structures.

The primary goal of bioinformatics is to increase the understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques (e.g., pattern recognition, data mining, machine learning algorithms, and visualization) to achieve this goal. Major research efforts in the field include sequence alignment, gene finding, genome assembly, drug design, drug discovery, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, genome-wide association studies and the modeling of evolution.

Introduction

Bioinformatics was applied in the creation and maintenance of a database to store biological information at the beginning of the "genomic revolution", such as nucleotide and amino acid sequences. Development of this type of database involved not only design issues but the development of complex interfaces whereby researchers could both access existing data as well as submit new or revised data.

In order to study how normal cellular activities are altered in different disease states, the biological data must be combined to form a comprehensive picture of these activities. Therefore, the field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data, including nucleotide and amino acid sequences, protein domains, and protein structures. The actual process of analyzing and interpreting data is referred to as computational biology. Important sub-disciplines within bioinformatics and computational biology include:

- the development and implementation of tools that enable efficient access to, and use and management of, various types of information.
- the development of new algorithms (mathematical formulas) and statistics with which to assess relationships among members of large data sets, such as methods to locate a gene within a sequence, predict protein structure

and/or function, and cluster protein sequences into families of related sequences.

Major research areas

Sequence analysis

Since the Phage Φ-X174 was sequenced in 1977, the DNA sequences of thousands of organisms have been decoded and stored in databases. This sequence information is analyzed to determine genes that encode polypeptides (proteins), RNA genes, regulatory sequences, structural motifs, and repetitive sequences. A comparison of genes within a species or between different species can show similarities between protein functions, or relations between species (the use of molecular systematics to construct phylogenetic trees). With the growing amount of data, it long ago became impractical to analyze DNA sequences manually. Today, computer programs such as BLAST are used daily to search the genomes of thousands of organisms, containing billions of nucleotides. These programs can compensate for mutations (exchanged, deleted or inserted bases) in the DNA sequence, in order to identify sequences that are related, but not identical. A variant of this sequence alignment is used in the sequencing process itself. The so-called shotgun sequencing technique (which was used, for example, by The Institute for Genomic Research to sequence the first bacterial genome, *Haemophilus influenzae*) does not produce entire chromosomes, but instead generates the sequences of many thousands of small DNA fragments (ranging from 35 to 900 nucleotides long, depending on the sequencing technology). The ends of these fragments overlap and, when aligned properly by a genome assembly program, can be used to reconstruct the complete genome. Shotgun sequencing yields sequence data quickly, but the task of assembling the fragments can be quite complicated for larger genomes. For a genome as large as the human genome, it may take many days of CPU time on large-memory, multiprocessor computers to assemble the fragments, and the resulting assembly will usually contain numerous gaps that have to be filled in later. Shotgun sequencing is the method of choice for virtually all genomes sequenced today, and genome assembly algorithms are a critical area of bioinformatics research.

Another aspect of bioinformatics in sequence analysis is annotation, which involves computational gene finding to search for protein-coding genes, RNA genes, and other functional sequences within a genome. Not all of the nucleotides within a genome are part of genes. Within the genome of higher organisms, large parts of the DNA do not serve any obvious purpose. This so-called junk DNA may, however, contain unrecognized functional elements. Bioinformatics helps to bridge the gap between genome and proteome projects--for example, in the use of DNA sequences for protein identification.

Genome annotation

In the context of genomics, **annotation** is the process of marking the genes and other biological features in a DNA sequence. The first genome annotation software system was designed in 1995 by Dr. Owen White, who was part of the team at The Institute for Genomic Research that sequenced and analyzed the first genome of a free-living organism to be decoded, the bacterium *Haemophilus influenzae*. Dr. White built a software system to find the genes (places in the DNA sequence that encode a protein), the transfer RNA, and other features, and to make initial assignments of function to those genes. Most current genome annotation systems work similarly, but the programs available for analysis of genomic DNA are constantly changing and improving.

Computational evolutionary biology

Evolutionary biology is the study of the origin and descent of species, as well as their change over time. Informatics has assisted evolutionary biologists in several key ways; it has enabled researchers to:

- trace the evolution of a large number of organisms by measuring changes in their DNA, rather than through physical taxonomy or physiological observations alone,
- more recently, compare entire genomes, which permits the study of more complex evolutionary events, such as gene duplication, horizontal gene transfer, and the prediction of factors important in bacterial speciation,
- build complex computational models of populations to predict the outcome of the system over time
- track and share information on an increasingly large number of species and organisms

Future work endeavours to reconstruct the now more complex tree of life.

The area of research within computer science that uses genetic algorithms is sometimes confused with computational evolutionary biology, but the two areas are not necessarily related.

Analysis of gene expression

The expression of many genes can be determined by measuring mRNA levels with multiple techniques including microarrays, expressed cDNA sequence tag (EST) sequencing, serial analysis of gene expression (SAGE) tag sequencing, massively parallel signature sequencing (MPSS), or various applications of multiplexed in-situ hybridization. All of these techniques are extremely noise-prone and/or subject to bias in the biological measurement, and a major research area in computational biology involves developing statistical tools to separate signal from noise in high-throughput gene expression studies. Such studies are often used to determine the genes implicated in a disorder: one might compare microarray data from cancerous epithelial cells to data from non-cancerous cells to determine the transcripts that are up-regulated and down-regulated in a particular population of cancer cells.

Analysis of regulation

Regulation is the complex orchestration of events starting with an extracellular signal such as a hormone and leading to an increase or decrease in the activity of one or more proteins. Bioinformatics techniques have been applied to explore various steps in this process. For example, promoter analysis involves the identification and study of sequence motifs in the DNA surrounding the coding region of a gene. These motifs influence the extent to which that region is transcribed into mRNA. Expression data can be used to infer gene regulation: one might compare microarray data from a wide variety of states of an organism to form hypotheses about the genes involved in each state. In a single-cell organism, one might compare stages of the cell cycle, along with various stress conditions (heat shock, starvation, etc.). One can then apply clustering algorithms to that expression data to determine which genes are co-expressed. For example, the upstream regions (promoters) of co-expressed genes can be searched for over-represented regulatory elements.

Analysis of protein expression

Protein microarrays and high throughput (HT) mass spectrometry (MS) can provide a snapshot of the proteins present in a biological sample. Bioinformatics is very much involved in making sense of protein microarray and HT MS data; the former approach faces similar problems as with microarrays targeted at mRNA, the latter involves the problem of matching large amounts of mass data against predicted masses from protein sequence databases, and the complicated statistical analysis of samples where multiple, but incomplete peptides from each protein are detected.

Analysis of mutations in cancer

In cancer, the genomes of affected cells are rearranged in complex or even unpredictable ways. Massive sequencing efforts are used to identify previously unknown point mutations in a variety of genes in cancer. Bioinformaticians continue to produce specialized automated systems to manage the sheer volume of sequence data produced, and they create new algorithms and software to compare the sequencing results to the growing collection of human genome sequences and germline polymorphisms. New physical detection technologies are employed, such as oligonucleotide microarrays to identify chromosomal gains and losses (called comparative genomic hybridization), and single-nucleotide polymorphism arrays to detect known *point mutations*. These detection methods simultaneously measure several hundred thousand sites throughout the genome, and when used in high-throughput to measure thousands of samples, generate terabytes of data per experiment. Again the massive amounts and new types of data generate new opportunities for bioinformaticians. The data is often found to contain considerable variability, or noise, and thus Hidden Markov model and change-point analysis methods are being developed to infer real copy number changes.

Another type of data that requires novel informatics development is the analysis of lesions found to be recurrent among many tumors .

Prediction of protein structure

Protein structure prediction is another important application of bioinformatics. The amino acid sequence of a protein, the so-called primary structure, can be easily determined from the sequence on the gene that codes for it. In the vast majority of cases, this primary structure uniquely determines a structure in its native environment. (Of course, there are exceptions, such as the bovine spongiform encephalopathy - aka Mad Cow Disease - prion.) Knowledge of this structure is vital in understanding the function of the protein. For lack of better terms, structural information is usually classified as one of *secondary*, *tertiary* and *quaternary* structure. A viable general solution to such predictions remains an open problem. As of now, most efforts have been directed towards heuristics that work most of the time.

One of the key ideas in bioinformatics is the notion of homology. In the genomic branch of bioinformatics, homology is used to predict the function of a gene: if the sequence of gene *A*, whose function is known, is homologous to the sequence of gene *B,* whose function is unknown, one could infer that B may share A's function. In the structural branch of bioinformatics, homology is used to determine which parts of a protein are important in structure formation and interaction with other proteins. In a technique called homology modeling, this information is used to predict the structure of a protein once the structure of a homologous protein is known. This currently remains the only way to predict protein structures reliably.

One example of this is the similar protein homology between hemoglobin in humans and the hemoglobin in legumes (leghemoglobin). Both serve the same purpose of transporting oxygen in the organism. Though both of these proteins have completely different amino acid sequences, their protein structures are virtually identical, which reflects their near identical purposes.

Other techniques for predicting protein structure include protein threading and *de novo* (from scratch) physics-based modeling.

See also: structural motif and structural domain.

Comparative genomics

The core of comparative genome analysis is the establishment of the correspondence between genes (orthology analysis) or other genomic features in different organisms. It is these intergenomic maps that make it possible to trace the evolutionary processes responsible for the divergence of two genomes. A multitude of evolutionary events acting at various organizational levels shape genome evolution. At the lowest level, point mutations affect individual nucleotides. At a higher level, large chromosomal segments undergo duplication, lateral transfer, inversion, transposition, deletion and insertion. Ultimately, whole genomes are involved in processes of hybridization, polyploidization and endosymbiosis, often leading to rapid speciation. The complexity of genome evolution poses many exciting challenges to developers of mathematical models and algorithms, who have recourse to a spectra of algorithmic, statistical and mathematical techniques, ranging from exact, heuristics, fixed parameter and approximation algorithms for problems based on parsimony models to Markov Chain Monte Carlo algorithms for Bayesian analysis of problems based on probabilistic models.

Many of these studies are based on the homology detection and protein families computation.

Modeling biological systems

Systems biology involves the use of computer simulations of cellular subsystems (such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks) to both analyze and visualize the complex connections of these cellular processes. Artificial life or virtual evolution attempts to understand evolutionary processes via the computer simulation of simple (artificial) life forms.

High-throughput image analysis

Computational technologies are used to accelerate or fully automate the processing, quantification and analysis of large amounts of high-information-content biomedical imagery. Modern image analysis systems augment an observer's ability to make measurements from a large or complex set of images, by improving accuracy, objectivity, or speed. A fully developed analysis system may completely replace the observer. Although these systems are not unique to biomedical imagery, biomedical imaging is becoming more important for both diagnostics and research. Some examples are:

- high-throughput and high-fidelity quantification and sub-cellular localization (high-content screening, cytohistopathology, Bioimage informatics)
- morphometrics
- clinical image analysis and visualization
- determining the real-time air-flow patterns in breathing lungs of living animals
- quantifying occlusion size in real-time imagery from the development of and recovery during arterial injury
- making behavioral observations from extended video recordings of laboratory animals
- infrared measurements for metabolic activity determination
- inferring clone overlaps in DNA mapping, e.g. the Sulston score

Protein-protein docking

In the last two decades, tens of thousands of protein three-dimensional structures have been determined by X-ray crystallography and Protein nuclear magnetic resonance spectroscopy (protein NMR). One central question for the biological scientist is whether it is practical to predict possible protein-protein interactions only based on these 3D shapes, without doing protein-protein interaction experiments. A variety of methods have been developed to tackle the Protein-protein docking problem, though it seems that there is still much work to be done in this field.

Software and tools

Software tools for bioinformatics range from simple command-line tools, to more complex graphical programs and standalone web-services available from various bioinformatics companies or public institutions.

Web services in bioinformatics

SOAP and REST-based interfaces have been developed for a wide variety of bioinformatics applications allowing an application running on one computer in one part of the world to use algorithms, data and computing resources on servers in other parts of the world. The main advantages derive from the fact that end users do not have to deal with software and database maintenance overheads.

Basic bioinformatics services are classified by the EBI into three categories: SSS (Sequence Search Services), MSA (Multiple Sequence Alignment) and BSA (Biological Sequence Analysis). The availability of these service-oriented bioinformatics resources demonstrate the applicability of web based bioinformatics solutions, and range from a collection of standalone tools with a common data format under a single, standalone or web-based interface, to integrative, distributed and extensible bioinformatics workflow management systems.

See also

- Bioinformatics companies
- Health informatics
- Computational biomodeling
- Computational genomics
- DNA sequencing theory
- Dot plot (bioinformatics)
- Functional genomics
- Margaret Oakley Dayhoff
- Metabolic network modelling
- Molecular design software
- Molecular modeling on GPU
- Morphometrics
- Protein-protein interaction prediction
- List of scientific journals in bioinformatics
- Nucleic acid simulation software

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- Dedicated issue of *Philosophical Transactions B* on Bioinformatics freely available (http://publishing.royalsociety.org/bioinformatics)
- Catalyzing Inquiry at the Interface of Computing and Biology (2005) CSTB report (http://www.nap.edu/catalog/11480.html)
- Calculating the Secrets of Life: Contributions of the Mathematical Sciences and computing to Molecular Biology (1995) (http://www.nap.edu/catalog/2121.html)
- Foundations of Computational and Systems Biology MIT Course (http://ocw.mit.edu/OcwWeb/Biology/7-91JSpring2004/LectureNotes/index.htm)
- Computational Biology: Genomes, Networks, Evolution Free MIT Course (http://compbio.mit.edu/6.047/)
- Algorithms for Computational Biology Free MIT Course (http://ocw.mit.edu/OcwWeb/Electrical-Engineering-and-Computer-Science/6-096Spring-2005/CourseHome/index.htm)
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External links

- Bioinformatics Organization (http://bioinformatics.org/)
- Bioinformatics Research Groups (http://www.google.com/Top/Science/Biology/Bioinformatics/Research_Groups/) - Google Directory
- EMBnet (http://www.embnet.org/)
- Open Bioinformatics Foundation (http://www.open-bio.org/)

Genomics

Genomics is a discipline in genetics concerning the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts. The field also includes studies of intragenomic phenomena such as heterosis, epistasis, pleiotropy and other interactions between loci and alleles within the genome. In contrast, the investigation of the roles and functions of single genes is a primary focus of molecular biology or genetics and is a common topic of modern medical and biological research. Research of single genes does not fall into the definition of genomics unless the aim of this genetic, pathway, and functional information analysis is to elucidate its effect on, place in, and response to the entire genome's networks.

For the United States Environmental Protection Agency, "the term "genomics" encompasses a broader scope of scientific inquiry associated technologies than when genomics was initially considered. A genome is the sum total of all an individual organism's genes. Thus, genomics is the study of all the genes of a cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels."[1]

History

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bioinformatic analyses in the 1970-1980s. A major branch of genomics is still concerned with sequencing the genomes of various organisms, but the knowledge of full genomes has created the possibility for the field of functional genomics, mainly concerned with patterns of gene expression during various conditions. The most important tools here are microarrays and bioinformatics. Study of the full set of proteins in a cell type or tissue, and the changes during various conditions, is called proteomics. A related concept is materiomics, which is defined as the study of the material properties of biological materials (e.g. hierarchical protein structures and materials, mineralized biological tissues, etc.) and their effect on the macroscopic function and failure in their biological context, linking processes, structure and properties at multiple scales through a materials science approach. The actual term 'genomics' is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) over beer at a meeting held in Maryland on the mapping of the human genome in 1986.

In 1972, Walter Fiers and his team at the Laboratory of Molecular Biology of the University of Ghent (Ghent, Belgium) were the first to determine the sequence of a gene: the gene for Bacteriophage MS2 coat protein.[2] In 1976, the team determined the complete nucleotide-sequence of bacteriophage MS2-RNA.[3] The first DNA-based genome to be sequenced in its entirety was that of bacteriophage Φ-X174; (5,368 bp), sequenced by Frederick Sanger in 1977.[4]

The first free-living organism to be sequenced was that of *Haemophilus influenzae* (1.8 Mb) in 1995, and since then genomes are being sequenced at a rapid pace.

As of September 2007, the complete sequence was known of about 1879 viruses [5] , 577 bacterial species and roughly 23 eukaryote organisms, of which about half are fungi. [6] Most of the bacteria whose genomes have been completely sequenced are problematic disease-causing agents, such as *Haemophilus influenzae*. Of the other sequenced species, most were chosen because they were well-studied model organisms or promised to become good models. Yeast (*Saccharomyces cerevisiae*) has long been an important model organism for the eukaryotic cell, while the fruit fly *Drosophila melanogaster* has been a very important tool (notably in early pre-molecular genetics). The worm *Caenorhabditis elegans* is an often used simple model for multicellular organisms. The zebrafish *Brachydanio rerio* is used for many developmental studies on the molecular level and the flower *Arabidopsis thaliana* is a model organism for flowering plants. The Japanese pufferfish (*Takifugu rubripes*) and the spotted green pufferfish (*Tetraodon nigroviridis*) are interesting because of their small and compact genomes, containing very little non-coding DNA compared to most species. [7] [8] The mammals dog (*Canis familiaris*), [9] brown rat (*Rattus*

norvegicus), mouse (*Mus musculus*), and chimpanzee (*Pan troglodytes*) are all important model animals in medical research.

Human genomics

A rough draft of the human genome was completed by the Human Genome Project in early 2001, creating much fanfare. By 2007 the human sequence was declared "finished" (less than one error in 20,000 bases and all chromosomes assembled). Display of the results of the project required significant bioinformatics resources. The sequence of the human reference assembly can be explored using the UCSC Genome Browser.

Bacteriophage genomics

Bacteriophages have played and continue to play a key role in bacterial genetics and molecular biology. Historically, they were used to define gene structure and gene regulation. Also the first genome to be sequenced was a bacteriophage. However, bacteriophage research did not lead the genomics revolution, which is clearly dominated by bacterial genomics. Only very recently has the study of bacteriophage genomes become prominent, thereby enabling researchers to understand the mechanisms underlying phage evolution. Bacteriophage genome sequences can be obtained through direct sequencing of isolated bacteriophages, but can also be derived as part of microbial genomes. Analysis of bacterial genomes has shown that a substantial amount of microbial DNA consists of prophage sequences and prophage-like elements. A detailed database mining of these sequences offers insights into the role of prophages in shaping the bacterial genome.[10]

Cyanobacteria genomics

At present there are 24 cyanobacteria for which a total genome sequence is available. 15 of these cyanobacteria come from the marine environment. These are six *Prochlorococcus* strains, seven marine *Synechococcus* strains, *Trichodesmium erythraeum* IMS101 and *Crocosphaera watsonii* WH8501. Several studies have demonstrated how these sequences could be used very successfully to infer important ecological and physiological characteristics of marine cyanobacteria. However, there are many more genome projects currently in progress, amongst those there are further *Prochlorococcus* and marine *Synechococcus* isolates, *Acaryochloris* and *Prochloron*, the N_2-fixing filamentous cyanobacteria *Nodularia spumigena*, *Lyngbya aestuarii* and *Lyngbya majuscula*, as well as bacteriophages infecting marine cyanobaceria. Thus, the growing body of genome information can also be tapped in a more general way to address global problems by applying a comparative approach. Some new and exciting examples of progress in this field are the identification of genes for regulatory RNAs, insights into the evolutionary origin of photosynthesis, or estimation of the contribution of horizontal gene transfer to the genomes that have been analyzed.[11]

See also

- Full Genome Sequencing
- Computational genomics
- Nitrogenomics
- Metagenomics
- Predictive Medicine
- Personal genomics
- Psychogenomics

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External links

- Genomics Directory (http://www.genomicsdirectory.com): A one-stop biotechnology resource center for bioentrepreneurs, scientists, and students
- Annual Review of Genomics and Human Genetics (http://arjournals.annualreviews.org/loi/genom/)
- BMC Genomics (http://www.biomedcentral.com/bmcgenomics/): A BMC journal on Genomics
- Genomics (http://www.genomics.co.uk/companylist.php): UK companies and laboratories* Genomics journal (http://www.elsevier.com/wps/find/journaldescription.cws_home/622838/description#description)
- Genomics and Quantitative Genetics (http://www.knoblauchpublishing.com): An international electronic, open access journal publishing, inter alia, genomics research.
- Genomics.org (http://genomics.org): An openfree wiki based Genomics portal
- NHGRI (http://www.genome.gov/): US government's genome institute
- Pharmacogenomics in Drug Discovery and Development (http://www.springer.com/humana+press/pharmacology+and+toxicology/book/978-1-58829-887-4), a book on pharmacogenomics, diseases, personalized medicine, and therapeutics
- Tishchenko P. D. Genomics: New Science in the New Cultural Situation (http://www.zpu-journal.ru/en/articles/detail.php?ID=342)
- Undergraduate program on Genomic Sciences (spanish) (http://www.lcg.unam.mx/): One of the first undergraduate programs in the world
- JCVI Comprehensive Microbial Resource (http://cmr.jcvi.org/)
- Pathema: A Clade Specific Bioinformatics Resource Center (http://pathema.jcvi.org/)
- KoreaGenome.org (http://koreagenome.org): The first Korean Genome published and the sequence is available freely.
- GenomicsNetwork (http://genomicsnetwork.ac.uk): Looks at the development and use of the science and technologies of genomics.
- Institute for Genome Sciences (http://www.igs.umaryland.edu/research_topics.php): Genomics research.
- Institute for Genome Sciences (http://www.igs.umaryland.edu/research_topics.php): Genomics research.

Computational genomics

Computational genomics refers to the use of computational analysis to decipher biology from genome sequences and related data [1] , including both DNA and RNA sequence as well as other "post-genomic" data (i.e. experimental data obtained with technologies that require the genome sequence, such as genomic DNA microarrays). As such, computational genomics may be regarded as a subset of bioinformatics, but with a focus on using whole genomes (rather than individual genes) to understand the principles of how the DNA of a species controls its biology at the molecular level and beyond. With the current abundance of massive biological datasets, computational studies have become one of the most important means to biological discovery.[2]

History

The roots of computational genomics are shared with those of bioinformatics. During the 1960s, Margaret Dayhoff and others at the National Biomedical Research Foundation assembled databases of homologous protein sequences for evolutionary study.[3] Their research developed a phylogenetic tree that determined the evolutionary changes that were required for a particular protein to change into another protein based on the underlying amino acid sequences. This led them to create a scoring matrix that assessed the likelihood of one protein being related to another.

Beginning in the 1980s, databases of genome sequences began to be recorded, but this presented new challenges in the form of searching and comparing the databases of gene information. Unlike text-searching algorithms that are used on websites such as google or Wikipedia, searching for sections of genetic similarity requires one to find strings that are not simply identical, but similar. This led to the development of the Needleman-Wunsch algorithm, which is a dynamic programming algorithm for comparing sets of amino acid sequences with each other by using scoring matrices derived from the earlier research by Dayhoff. Later, the BLAST algorithm was developed for performing fast, optimized searches of gene sequence databases. BLAST and its derivatives are probably the most widely-used algorithms for this purpose.[4]

The emergence of the phrase "computational genomics" coincides with the availability of complete sequenced genomes in the mid-to-late 1990's. The first meeting of the Annual Conference on Computational Genomics was organized by scientists from The Institute for Genomic Research (TIGR) in 1998, providing a forum for this speciality and effectively distinguishing this area of science from the more general fields of Genomics or Computational Biology.[5] [6] The first use of this term in scientific literature, according to MEDLINE abstracts, was just one year earlier in Nucleic Acids Research.[7] . The final Computational Genomics conference was held in 2006, featuring a keynote talk by Nobel Laureate Barry Marshall, co-discoverer of the link between Helicobacter pylori and stomach ulcers. As of 2010, the leading conferences in the field include Intelligent Systems for Molecular Biology (ISMB), RECOMB, and the Cold Spring Harbor Laboratory and Sanger Institute's meetings titled "Biology of Genomes" and "Genome Informatics".

The development of computer-assisted mathematics (using products such as Mathematica or Matlab) has helped engineers, mathematicians and computer scientists to start operating in this domain, and a public collection of case studies and demonstrations is growing, ranging from whole genome comparisons to gene expression analysis.[8] . This has increased the introduction of different ideas, including concepts from systems and control, information theory, strings analysis and data mining. It is anticipated that computational approaches will become and remain a standard topic for research and teaching, while students fluent in both topics start being formed in the multiple courses created in the past few years.

Contributions of computational genomics research to biology

Contributions of computational genomics research to biology include [2] :

- discovering subtle patterns in genomic sequences
- proposing cellular signalling networks
- proposing mechanisms of genome evolution
- predict precise locations of all human genes using comparative genomics techniques with several mammalian and vertebrate species
- predict conserved genomic regions that are related to early embryonic development
- discover potential links between repeated sequence motifs and tissue-specific gene expression
- measure regions of genomes that have undergone unusually rapid evolution

See also

- Bioinformatics
- Biowiki
- Computational biology
- Genomics
- Microarray
- BLAST
- Computational epigenetics

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[5] [backPid]=67&cHash=fd69079f5e The 7th Annual Conference on Computational Genomics (2004) (http://www.jcvi.org/cms/press/press-releases/full-text/archive/2004//article/computational-genomics-conference-to-attract-leading-scientists/?tx_ttnews)

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External links

- Harvard Extension School Biophysics 101, Genomics and Computational Biology, http://www.courses.fas.harvard.edu/~bphys101/info/syllabus.html
- University of Bristol course in Computational Genomics, http://www.computational-genomics.net/

Proteomics

Robotic preparation of MALDI mass spectrometry samples on a sample carrier.

Proteomics is the large-scale study of proteins, particularly their structures and functions.[1] [2] Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells. The term "proteomics" was first coined in 1997[3] to make an analogy with genomics, the study of the genes. The word "proteome" is a blend of "**prote**in" and "gen**ome**", and was coined by Marc Wilkins in 1994 while working on the concept as a PhD student.[4] [5] The proteome is the entire complement of proteins,[4] including the modifications made to a particular set of proteins, produced by an organism or system. This will vary with time and distinct requirements, or stresses, that a cell or organism undergoes.

Complexity of the problem

After genomics, proteomics is considered the next step in the study of biological systems. It is much more complicated than genomics mostly because while an organism's genome is more or less constant, the proteome differs from cell to cell and from time to time. This is because distinct genes are expressed in distinct cell types. This means that even the basic set of proteins which are produced in a cell needs to be determined.

In the past this was done by mRNA analysis, but this was found not to correlate with protein content.[6] [7] It is now known that mRNA is not always translated into protein,[8] and the amount of protein produced for a given amount of mRNA depends on the gene it is transcribed from and on the current physiological state of the cell. Proteomics confirms the presence of the protein and provides a direct measure of the quantity present.

Post-translational modifications

Not only does the translation from mRNA cause differences, many proteins are also subjected to a wide variety of chemical modifications after translation. A lot of these post-translational modifications are critical to the protein's function.

Phosphorylation

One such modification is phosphorylation, which happens to many enzymes and structural proteins in the process of cell signaling. The addition of a phosphate to particular amino acids—most commonly serine and threonine[9] mediated by serine/threonine kinases, or more rarely tyrosine mediated by tyrosine kinases—causes a protein to become a target for binding or interacting with a distinct set of other proteins that recognize the phosphorylated domain.

Because protein phosphorylation is one of the most-studied protein modifications many "proteomic" efforts are geared to determining the set of phosphorylated proteins in a particular cell or tissue-type under particular circumstances. This alerts the scientist to the signaling pathways that may be active in that instance.

Ubiquitination

Ubiquitin is a small protein that can be affixed to certain protein substrates by enzymes called E3 ubiquitin ligases. Determining which proteins are poly-ubiquitinated can be helpful in understanding how protein pathways are regulated. This is therefore an additional legitimate "proteomic" study. Similarly, once it is determined what substrates are ubiquitinated by each ligase, determining the set of ligases expressed in a particular cell type will be helpful.

Additional modifications

Listing all the protein modifications that might be studied in a "Proteomics" project would require a discussion of most of biochemistry; therefore, a short list will serve here to illustrate the complexity of the problem. In addition to phosphorylation and ubiquitination, proteins can be subjected to (among others) methylation, acetylation, glycosylation, oxidation and nitrosylation. Some proteins undergo ALL of these modifications, often in time-dependent combinations, aptly illustrating the potential complexity one has to deal with when studying protein structure and function.

Distinct proteins are made under distinct settings

Even if one is studying a particular cell type, that cell may make different sets of proteins at different times, or under different conditions. Furthermore, as mentioned, any one protein can undergo a wide range of post-translational modifications.

Therefore a "proteomics" study can become quite complex very quickly, even if the object of the study is very restricted. In more ambitious settings, such as when a biomarker for a tumor is sought - when the proteomics scientist is obliged to study sera samples from multiple cancer patients - the amount of complexity that must be dealt with is as great as in any modern biological project.

Limitations to genomic study

Scientists are very interested in proteomics because it gives a much better understanding of an organism than genomics. First, the level of transcription of a gene gives only a rough estimate of its level of expression into a protein. An mRNA produced in abundance may be degraded rapidly or translated inefficiently, resulting in a small amount of protein. Second, as mentioned above many proteins experience post-translational modifications that profoundly affect their activities; for example some proteins are not active until they become phosphorylated. Methods such as phosphoproteomics and glycoproteomics are used to study post-translational modifications. Third, many transcripts give rise to more than one protein, through alternative splicing or alternative post-translational modifications. Fourth, many proteins form complexes with other proteins or RNA molecules, and only function in the presence of these other molecules. Finally, protein degradation rate plays an important role in protein content.[10]

Methods of studying proteins

Determining proteins which are post-translationally modified

One way in which a particular protein can be studied is to develop an antibody which is specific to that modification. For example, there are antibodies which only recognize certain proteins when they are tyrosine-phosphorylated, known as phospho-specific antibodies; also, there are antibodies specific to other modifications. These can be used to determine the set of proteins that have undergone the modification of interest.

For sugar modifications, such as glycosylation of proteins, certain lectins have been discovered which bind sugars. These too can be used.

A more common way to determine post-translational modification of interest is to subject a complex mixture of proteins to electrophoresis in "two-dimensions", which simply means that the proteins are electrophoresed first in one direction, and then in another... this allows small differences in a protein to be visualized by separating a modified protein from its unmodified form. This methodology is known as "two-dimensional gel electrophoresis".

Recently, another approach has been developed called PROTOMAP which combines SDS-PAGE with shotgun proteomics to enable detection of changes in gel-migration such as those caused by proteolysis or post translational modification.

Determining the existence of proteins in complex mixtures

Classically, antibodies to particular proteins or to their modified forms have been used in biochemistry and cell biology studies. These are among the most common tools used by practicing biologists today.

For more quantitative determinations of protein amounts, techniques such as ELISAs can be used.

For proteomic study, more recent techniques such as matrix-assisted laser desorption/ionization (MALDI) have been employed for rapid determination of proteins in particular mixtures and increasingly electrospray ionization (ESI).

Establishing protein-protein interactions

Most proteins function in collaboration with other proteins, and one goal of proteomics is to identify which proteins interact. This is especially useful in determining potential partners in cell signaling cascades.

Several methods are available to probe protein-protein interactions. The traditional method is yeast two-hybrid analysis. New methods include protein microarrays, immunoaffinity chromatography followed by mass spectrometry, dual polarisation interferometry and experimental methods such as phage display and computational methods

Practical applications of proteomics

One of the most promising developments to come from the study of human genes and proteins has been the identification of potential new drugs for the treatment of disease. This relies on genome and proteome information to identify proteins associated with a disease, which computer software can then use as targets for new drugs. For example, if a certain protein is implicated in a disease, its 3D structure provides the information to design drugs to interfere with the action of the protein. A molecule that fits the active site of an enzyme, but cannot be released by the enzyme, will inactivate the enzyme. This is the basis of new drug-discovery tools, which aim to find new drugs to inactivate proteins involved in disease. As genetic differences among individuals are found, researchers expect to use these techniques to develop personalized drugs that are more effective for the individual.

A computer technique which attempts to fit millions of small molecules to the three-dimensional structure of a protein is called "virtual ligand screening". The computer rates the quality of the fit to various sites in the protein, with the goal of either enhancing or disabling the function of the protein, depending on its function in the cell. A

good example of this is the identification of new drugs to target and inactivate the HIV-1 protease. The HIV-1 protease is an enzyme that cleaves a very large HIV protein into smaller, functional proteins. The virus cannot survive without this enzyme; therefore, it is one of the most effective protein targets for killing HIV.

Biomarkers

The FDA defines a biomarker as, "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".

Understanding the proteome, the structure and function of each protein and the complexities of protein-protein interactions will be critical for developing the most effective diagnostic techniques and disease treatments in the future.

An interesting use of proteomics is using specific protein biomarkers to diagnose disease. A number of techniques allow to test for proteins produced during a particular disease, which helps to diagnose the disease quickly. Techniques include western blot, immunohistochemical staining, enzyme linked immunosorbent assay (ELISA) or mass spectrometry.

Current research methodologies

There are many approaches to attempting to characterize the human proteome, which is estimated to exceed 100,000 unique forms, 25,000 genes plus post-translational modifications.

See also

- Proteomic chemistry
- Bioinformatics
- Cytomics
- Genomics
- List of omics topics in biology
- Metabolomics
- Lipidomics
- Shotgun proteomics
- Top-down proteomics
- Bottom-up proteomics
- Systems biology
- Transcriptomics
- Phosphoproteomics
- PEGylation
- Functional genomics
- Activity based proteomics

Protein databases

- UniProt
- Protein Information Resource (PIR)
- Swiss-Prot
- Protein Data Bank (PDB)
- National Center for Biotechnology Information (NCBI)
- Human Protein Reference Database
- Proteomics Identifications Database (PRIDE)
- Proteopedia The collaborative, 3D encyclopedia of proteins and other molecules.

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External links

- Proteomics (http://www.dmoz.org//Science/Biology/Biochemistry_and_Molecular_Biology/Biomolecules/Proteins_and_Enzymes/Proteomics/) at the Open Directory Project

Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell[1] . The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments[2] .

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation[1] . Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

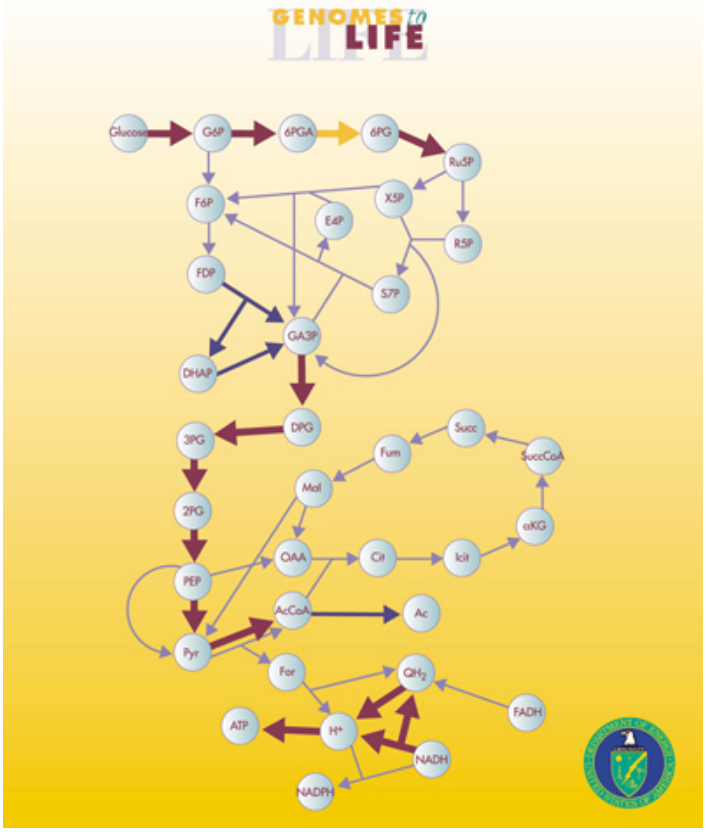
The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations[2] These experiments include:

- Two-hybrid screening
- Tandem Affinity Purification
- X-ray tomography
- Optical fluorescence microscopy

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified [3] .

Also there have been recent systematic attempts to explore the human interactome[1] and [4] .



Metabolic Network Model for Escherichia coli.

Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Ineractomes are not nearly complete with perhaps the exception of *S. cerivisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.
- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

See also

- Interaction network
- Proteomics
- Metabolic network
- Metabolic network modelling
- Metabolic pathway
- Genomics
- Mathematical biology
- Systems biology

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External links

- Interactomics.org (http://interactomics.org). A dedicated interactomics web site operated under BioLicense.
- Interactome.org (http://interactome.org). An interactome wiki site.
- PSIbase (http://psibase.kobic.re.kr) Structural Interactome Map of all Proteins.
- Omics.org (http://omics.org). An omics portal site that is openfree (under BioLicense)
- Genomics.org (http://genomics.org). A Genomics wiki site.
- Comparative Interactomics analysis of protein family interaction networks using PSIMAP (protein structural interactome map) (http://bioinformatics.oxfordjournals.org/cgi/content/full/21/15/3234)
- Interaction interfaces in proteins via the Voronoi diagram of atoms (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TYR-4KXVD30-2&_user=10&_coverDate=11/30/2006&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=8361bf3fe7834b4642cdda3b979de8bb)
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